Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry

Stereoselective Synthesis of Hydroxy Stilbenoids and Styrenes by Atom-efficient Olefination with Thiophthalides

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Supplementary Information

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General Remarks:

Melting points were determined in open-end capillary tubes and are uncorrected. Solvents were dried and distilled following the standard procedures. TLC was carried out on pre-coated plates (Merck silica gel 60, GF254), and the spots were visualized with UV and fluorescent light. Column chromatography was performed on silica gel (60-120 or 230-400 mesh). ^{1}H and ^{13}C NMR spectra for the compounds were recorded with 200 and 400 spectrometers. IR spectra were recorded on a FT-IR using KBr pellet on a Thermo Nicolet Nexus 870 FT-IR spectrophotometer. Mass spectra were taken using a VG Autospec M mass spectrometer.

General synthesis of thiophthalides:

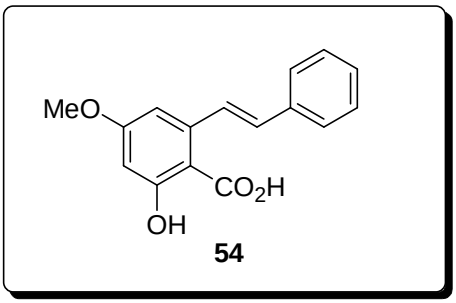
To a solution of an *ortho* tolurate (58 mmol) in carbon tetrachloride (130 mL) charged with AIBN (18 mg) was added *N*-bromosuccinimide (58 mmol). The mixture was heated at reflux until all the starting material completely disappeared. The mixture was then cooled to 0 °C, filtered and washed with carbon tetrachloride. The combined filtrate was then concentrated under reduced pressure. The resulting residue was dissolved in dry acetone (60 mL) and thiourea (55 mmol) was added to it. The mixture was then heated at 80 °C for 5-6 h. Evaporation of acetone yielded thiouronium salt which was directly treated with an aqueous solution of $NaHCO_3$ (4.5 gm in 50 mL of water) under an inert atmosphere at 90°C for 2 -3 h and then acidified with dil. HCl. The residue was then extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude product. This was then purified by column chromatography on silica gel to furnish pure thiophthalide.

General procedure for the decarboxylation:

The crude acid (1 mmol) was dissolved in minimum volume of methanol (~ 1 mL) and refluxed with 10 mL 30% aq KOH solution until full consumption of the starting acid. The mixture was acidified with 20% HCl and extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude product. This was then purified by column chromatography on silica gel.

Detailed procedures for the natural product synthesis sequences:

Synthesis of 3-hydroxy-5-methoxystilbene-2-carboxylic acid (**54**):



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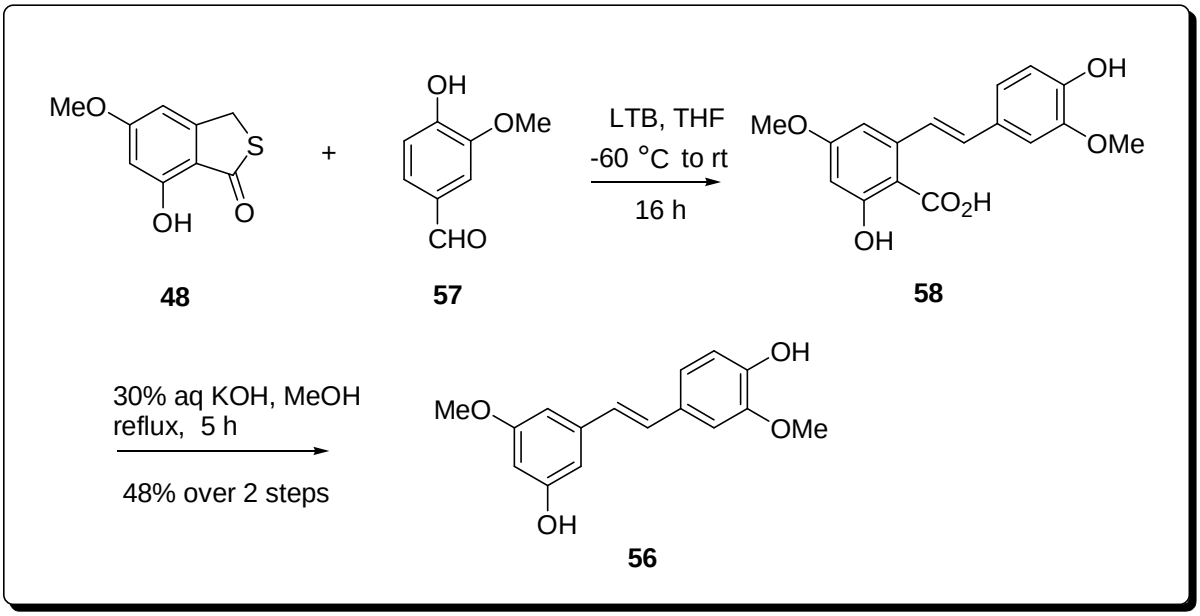
To a suspension of LTB (486 mg, 6 mmol) in dry THF (5 mL) at - 60 °C under an inert atmosphere was added a solution of thiophthalide **48** (196 mg, 1 mmol) in dry THF (5 mL). The resulting solution was stirred at - 60 °C for 30 min after which a solution of benzaldehyde (**55)** (424 mg, 4 mmol) in dry THF (5 mL) was added to it. The cooling bath was removed after about 30 min at - 60 °C and the reaction mixture was brought to room temperature and further stirred for 16 h. The reaction was then quenched with 6 N HCl, and THF removed under reduced pressure. The residue was then extracted with ethyl acetate (3 × 50 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude product. This was then purified by column chromatography on silica gel to obtain pure 3-hydroxy-5-methoxystilbene-2-carboxylic acid (**54**) in 67% yield.

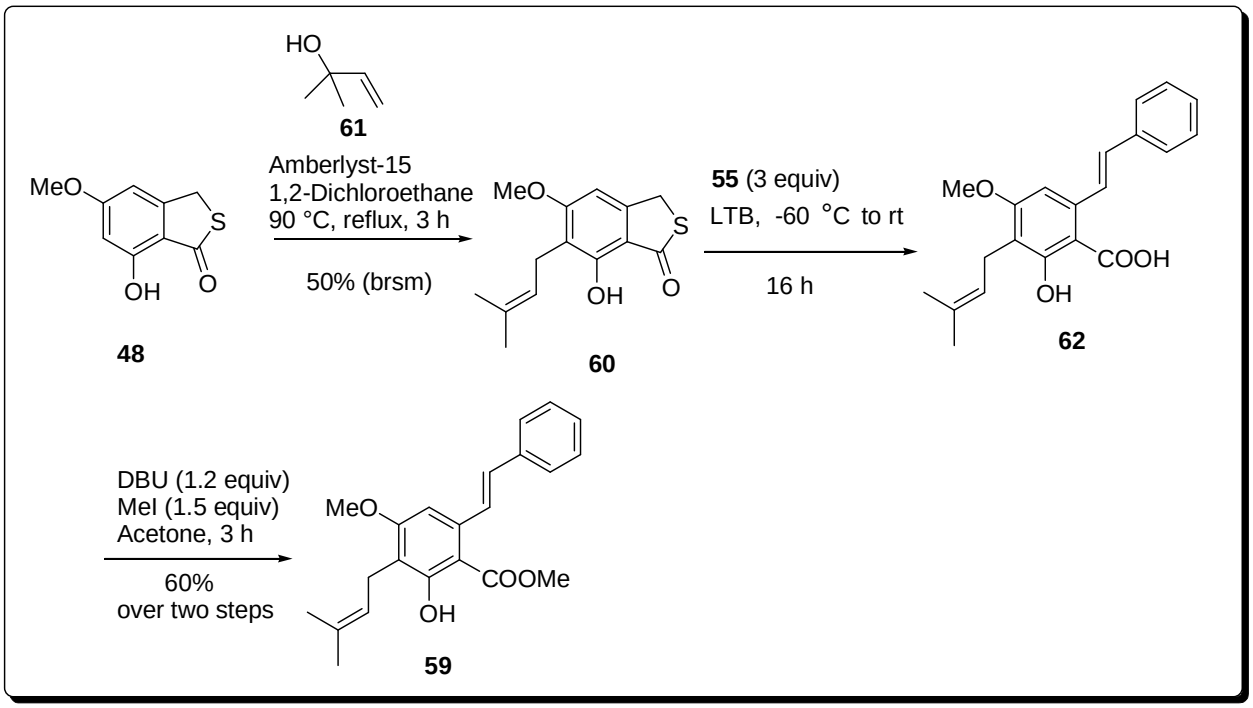
Synthesis of 3',4-dihydroxy-3,5'-dimethoxystilbene (**56**):



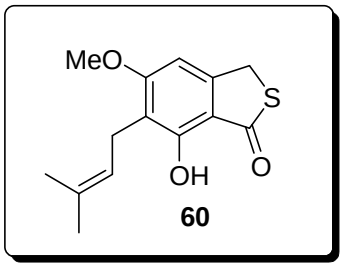
To a suspension of LTB (1830 mg, 22.62 mmol) in dry THF (15 mL) at - 60 °C under an inert atmosphere was added a solution of thiophthalide **48** (740 mg, 3.77 mmol) in dry THF (8 mL). The resulting solution was stirred at - 60 °C for 30 min after which a solution of vanillin (**57**) (545 mg, 3.58 mmol) in dry THF (5 mL) was added to it. The cooling bath was removed after about 30 min at - 60 °C, the reaction mixture was brought to room temperature and further stirred for 24 h. The reaction was then quenched with 6 N HCl, and THF removed under reduced pressure. The residue was then extracted with ethyl acetate (3 × 75 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude acid **58** along with unreacted starting materials. The starting materials were then removed by column chromatography on silica gel to obtain crude acid **58**.

The acid **58** was dissolved in 2 mL of methanol and refluxed with 30 mL 30% aq KOH solution for 9 h. Then it was acidified with 20% HCl and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude product. This was then purified by column chromatography on silica gel to furnish pure 3',4-dihydroxy-3,5'-dimethoxystilbene (**56**) (467 mg) in 48% yield over two steps.

Synthesis of methyl cajaninstilbene carboxylate (**59**):



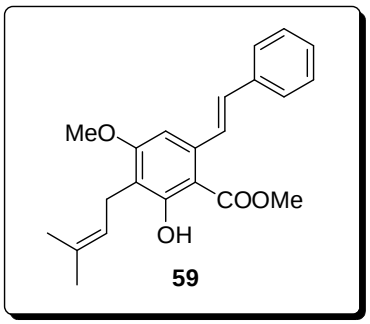
7-Hydroxy-5-methoxy-6-(3-methylbut-2-enyl)-3*H*-benzo[*c*]thiophen-1-one (**60**):



To a stirred suspension of thiophthalide **48** (3.0 g, 15.3 mmol) and Amberlyst-15 (250 mg) in 1,2-dichloroethane (30 mL), was added 1,1-dimethylallyl alcohol **61** (2 mL, 19.16 mmol) and the resulting reaction mixture refluxed at 90 °C for 3 h. The reaction mixture was

then cooled to room temperature and filtered before it was concentrated under reduced pressure. It was then purified by performing column chromatography on silica gel to give **60** (400 mg, 1.51 mmol) in 10% yield along with the unreacted thiophthalide **48** (2.4 g).

Methyl 2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)-6-styrylbenzoate (**59**):



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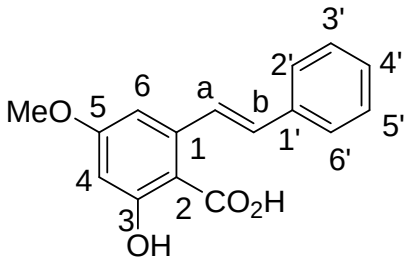
To a suspension of LTB (200 mg, 2.4 mmol) in dry THF (5 mL) at - 60 °C under an inert atmosphere was added a solution of thiophthalide **60** (110 mg, 0.41 mmol) in dry THF (3 mL). The resulting solution was stirred at - 60 °C for 30 min after which a solution of benzaldehyde (**55**) (0.13 mL, 1.25 mmol) in dry THF (3 mL) was added to it. The cooling bath was removed after about 30 min at - 60 °C, The reaction mixture was brought to room temperature and further stirred for 24 h and then quenched with 6 N HCl, and THF removed under reduced pressure. The residue was then extracted with ethyl acetate (3 × 15 mL). The combined extracts were washed with brine (3 × 1/3 vol.), dried (Na_2SO_4) and concentrated to provide the crude styryl acid **62**.

DBU (0.08 mL, 0.5 mmol) was added to a stirred solution of the crude acid in dry acetone (5 mL) at rt and the reaction was stirred for 15 min. Iodomethane (0.04 mL, 0.62 mmol) was added to the mixture over a period of 5 min, and stirring was continued for 3 h at rt. The reaction mixture was concentrated and diluted with ethyl acetate (20 mL). The resulting solution was washed successively with water (5 mL), saturated aqueous solution of sodium thiosulfate (5 mL), and brine (5 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography on silica gel to afford the corresponding pure ester **59** (86 mg, 60% yield).

Comparison of the NMR data of synthetic and natural products:

3-hydroxy-5-methoxystilbene-2-carboxylic acid (**54**):



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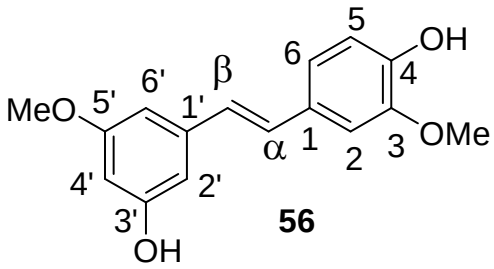
^{1}H	^{1}H chemical shifts (δ) (reported)[1]	^{13}C	^{13}C chemical shifts (δ) (reported)[1]
	7.93 (7.89)	**1**	143.2 (143.7)
	7.50 (7.50)	**2**	104.2 (104.3)
	7.40-7.26 (7.35-7.26)	**3**	165.6 (165.4)
	6.82 (6.84)	**4**	100.2 (100.4)
	6.65 (6.66)	**5**	163.9 (164.3)
	6.43 (6.43)	**6**	107.1 (107.6)
		1'	137.4 (137.8)
		2'. 6'	126.7 (126.9)
		3', 5'	128.6 (128.8)
		4'	127.6 (127.9)
		a	130.2 (130.3)
		b	130.5 (130.9)
$C\underline{H}_3O$-	3.87 (3.86)	$\underline{C}H_3O$-	55.4 (55.6)

COOH	12.47 (not observed)	COOH	173.7 (173.4)

3',4-dihydroxy-3,5'-dimethoxystilbene (**56**):



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^{1}H	^{1}H chemical shifts (δ) (reported)[2]	^{13}C	^{13}C chemical shifts (δ) (reported)[2]
	7.23 (7.22)	**1**	130.7 (129.7)
	7.09 (7.10)	**2**	110.4 (109.5)
	7.04 (7.02)	**3**	147.9 (147.1)
	6.95 (6.97)	**4**	148.9 (148.0)
	6.82 (6.82)	**5**	116.3 (115.4)
	6.64 (6.63)	**6**	121.6 (120.7)
	6.64 (6.62)	**1'**	141.2 (140.3)
	6.32 (6.31)	**2'**	107.0 (106.1)
		3'	162.4 (161.5)
		4'	101.7 (100.8)
HO-	8.38 (not observed)	**5'**	159.9 (159.1)
HO-	7.76 (not observed)	**6'**	104.2 (103.2)
		α	130.1 (129.2)

		β	127.2 (126.3)
CH_3O-	3.89 (3.89)	CH_3O-	56.6 (not reported)[2]
CH_3O-	3.77 (3.77)	CH_3O-	55.8 (not reported)[2]

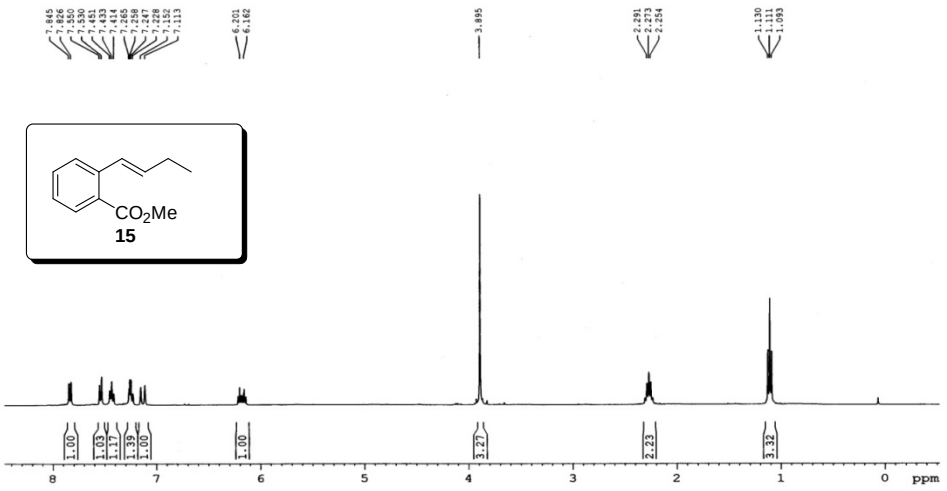
References:

1. Y. Ohwaki, J. Ogino and K. Shibano, *Soil Sci. Plant. Nutr*., 1993, **39**, 55.

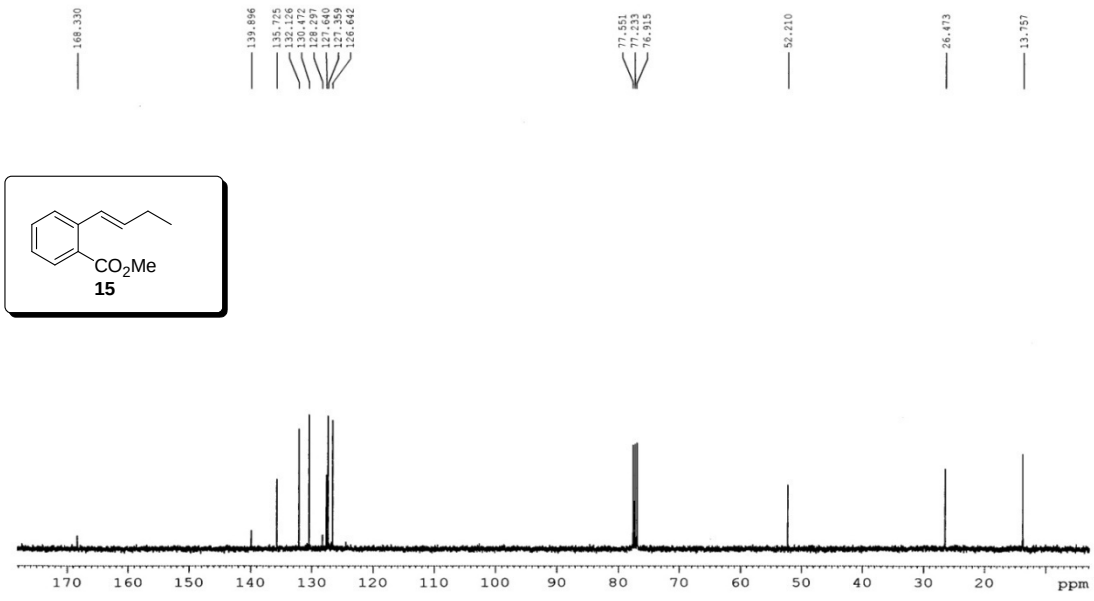
2. A. Silayoa, B. T. Ngadjuib and B. M. Abegaz, *Phytochemistry*, 1999, **52**, 947.

Methyl 2-But-1-enyl-benzoate (**15**):

^{1}H NMR (400MHz, $CDCl_3$):

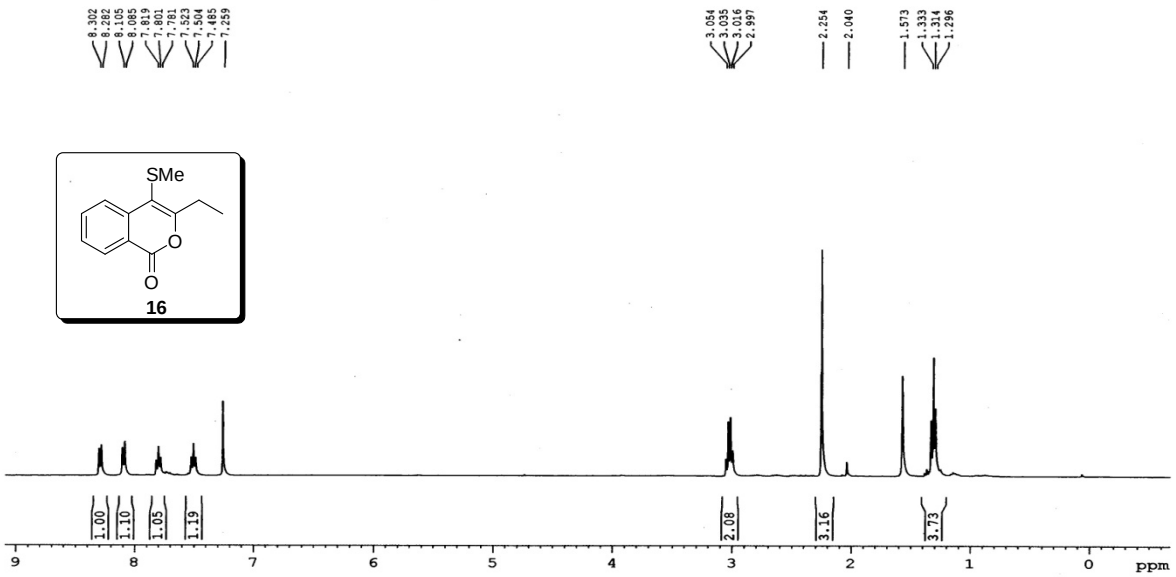


^{13}C NMR (100 MHz, $CDCl_3$)**:**

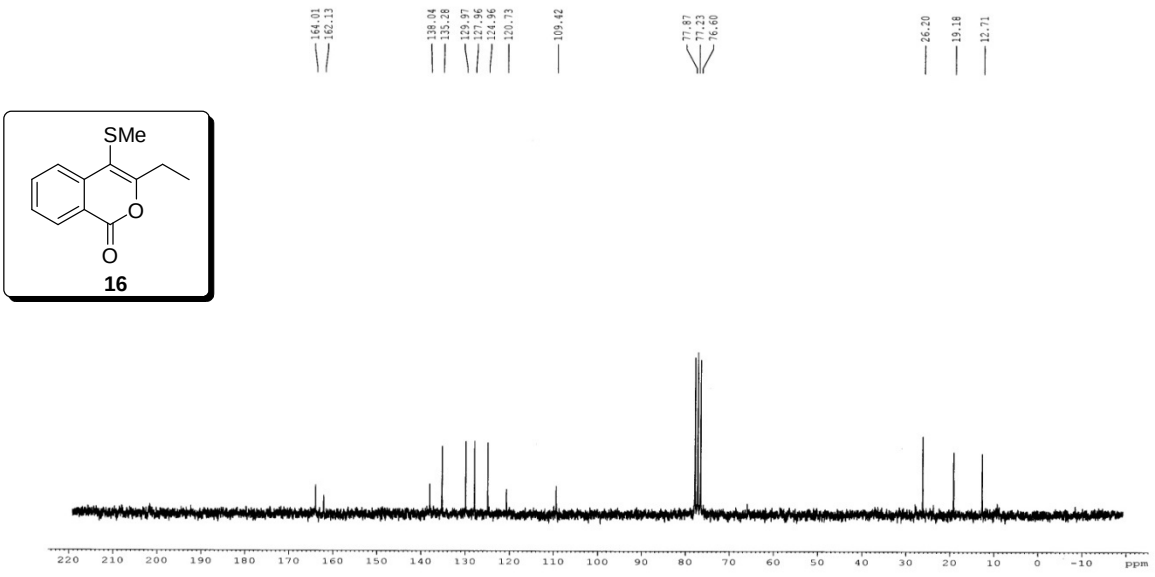


3-Ethyl-4 methylsulfanyl-isochromen-1-one (**16**):

^{1}H NMR (400MHz, $CDCl_3$):

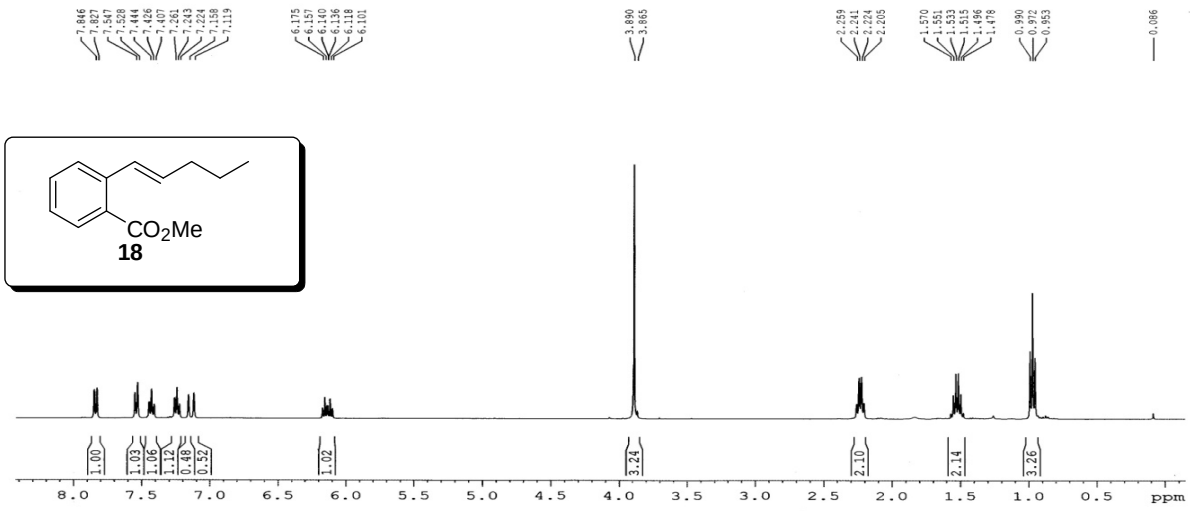


^{13}C NMR (100 MHz, $CDCl_3$):

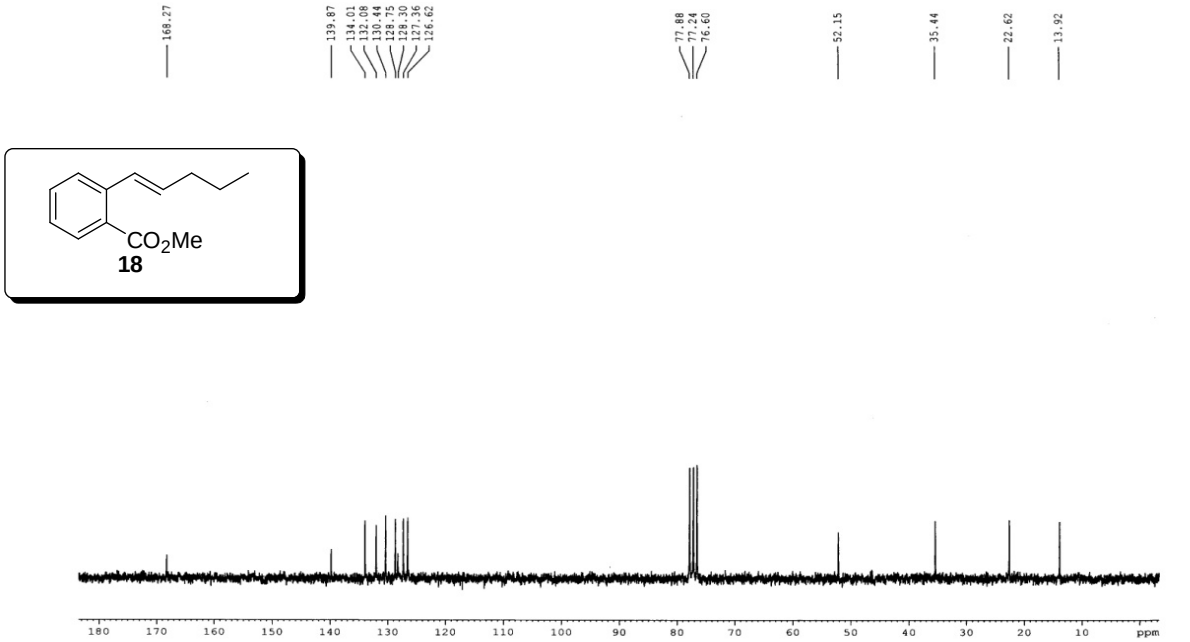


Methyl 2-Pent-1-enyl-benzoate (**18**):

^{1}H NMR (400MHz, $CDCl_3$):

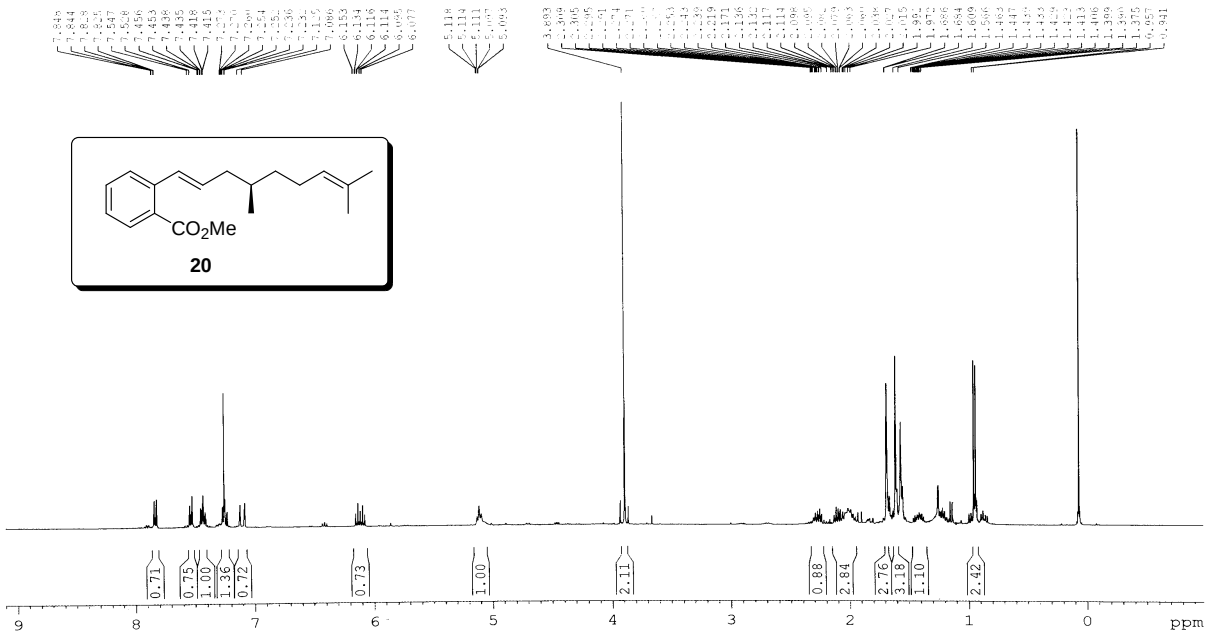


^{13}C NMR (100 MHz, $CDCl_3$):

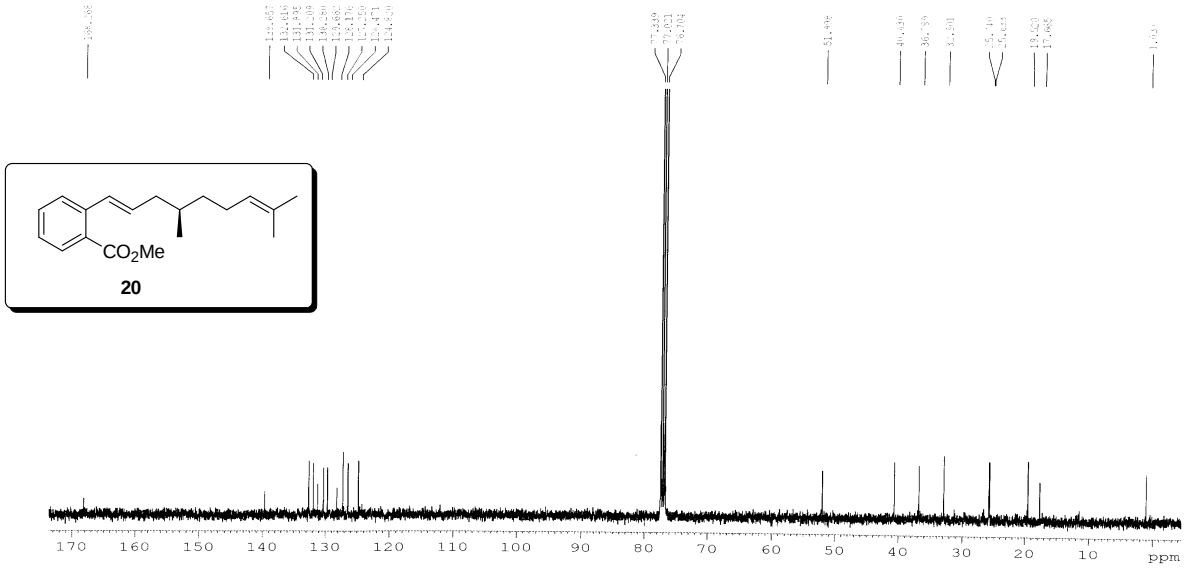


Methyl 2-(4,8-Dimethyl-nona-1,7-dienyl)benzoate (**20**):

^{1}H NMR (400MHz, $CDCl_3$):

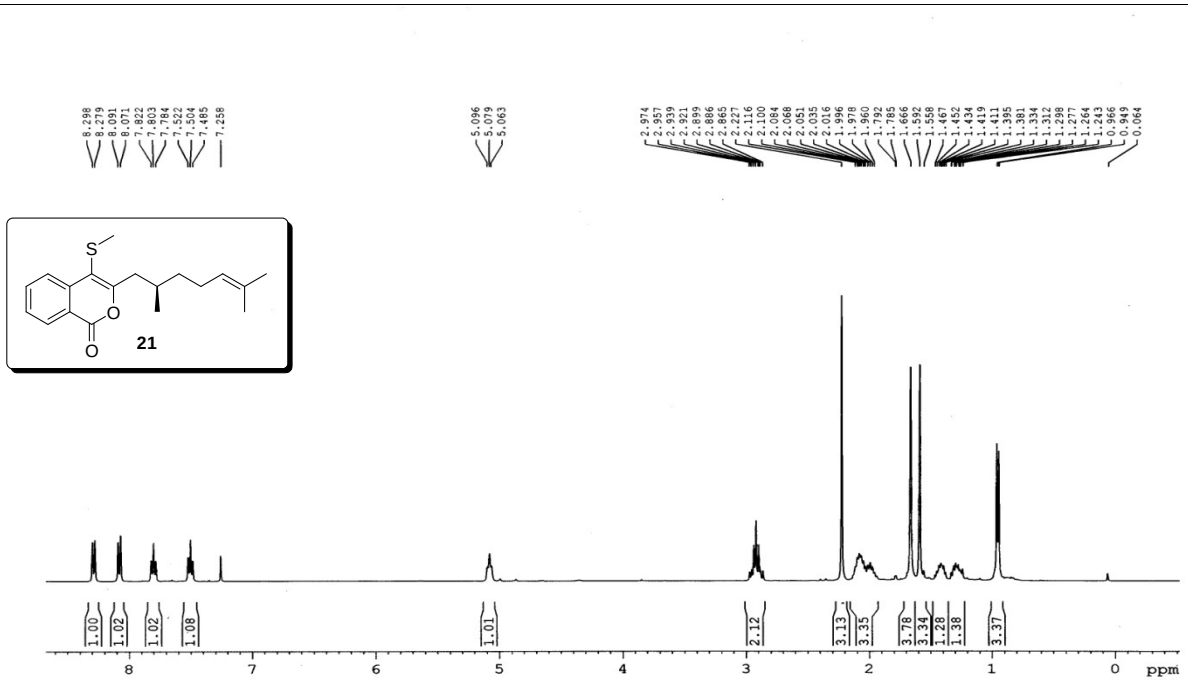


^{13}C NMR (100 MHz, $CDCl_3$):

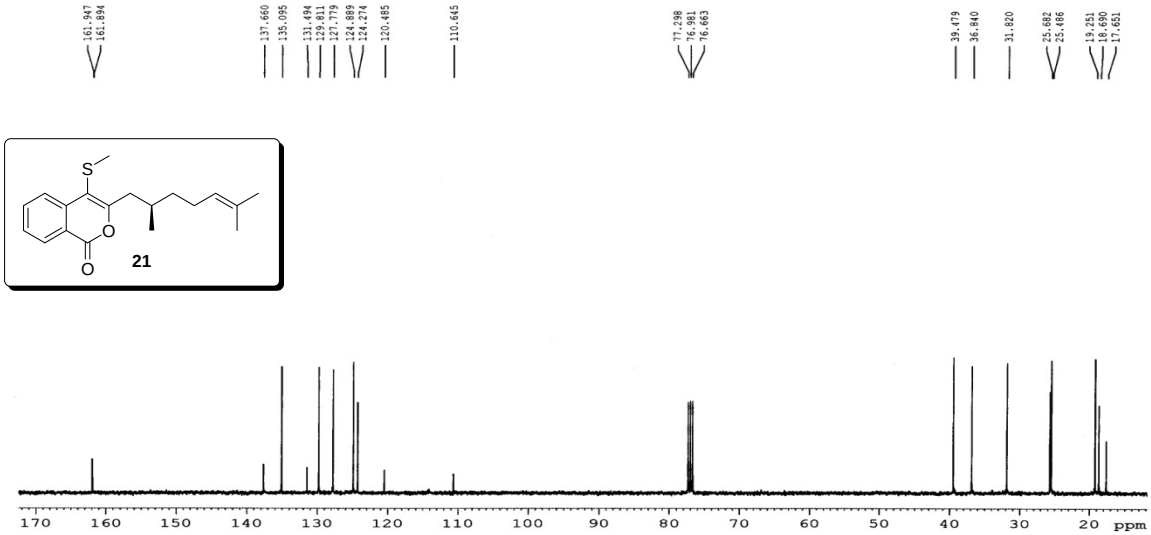


3-(2,6-Dimethyl-hept-5-enyl)-4-methylsulfanylisochromen-1-one (**21**):

^{1}H NMR (400MHz, $CDCl_3$,):

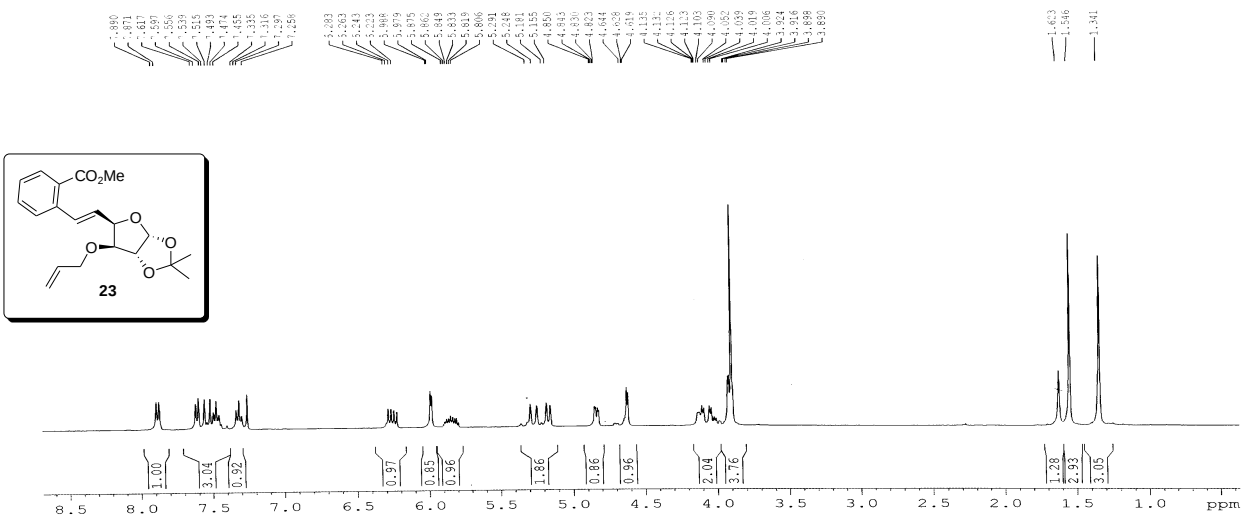


^{13}C NMR (100 MHz, $CDCl_3$):

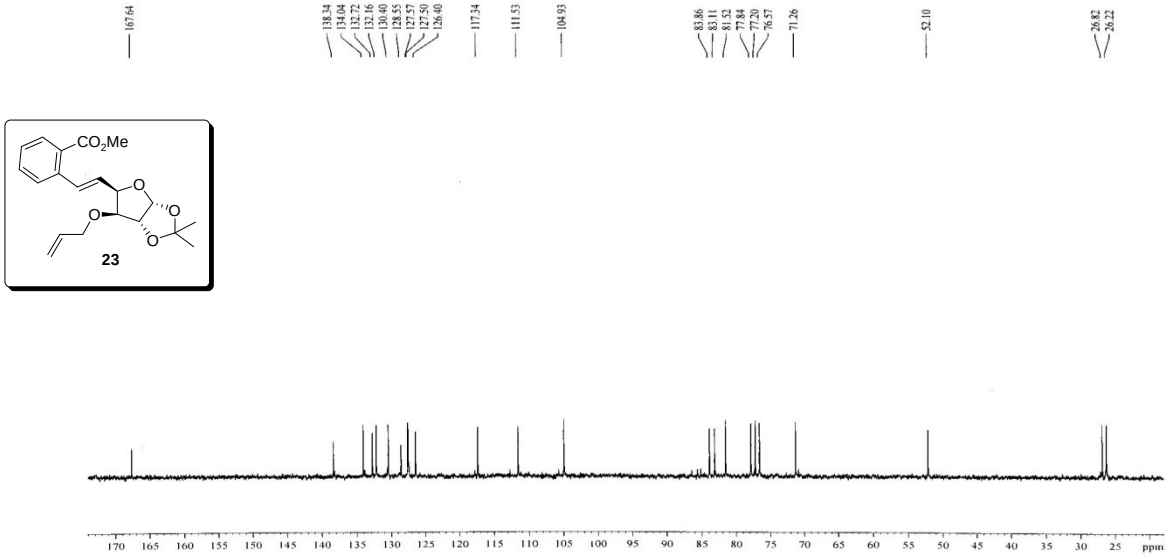


Methyl 2-[2-(6-Allyloxy-2,2-dimethyl-tetrahydro-furo[2,3-*d*][1,3]dioxol-5-yl)-vinyl]benzoate (**23**):

^{1}H NMR (400MHz, $CDCl_3$):

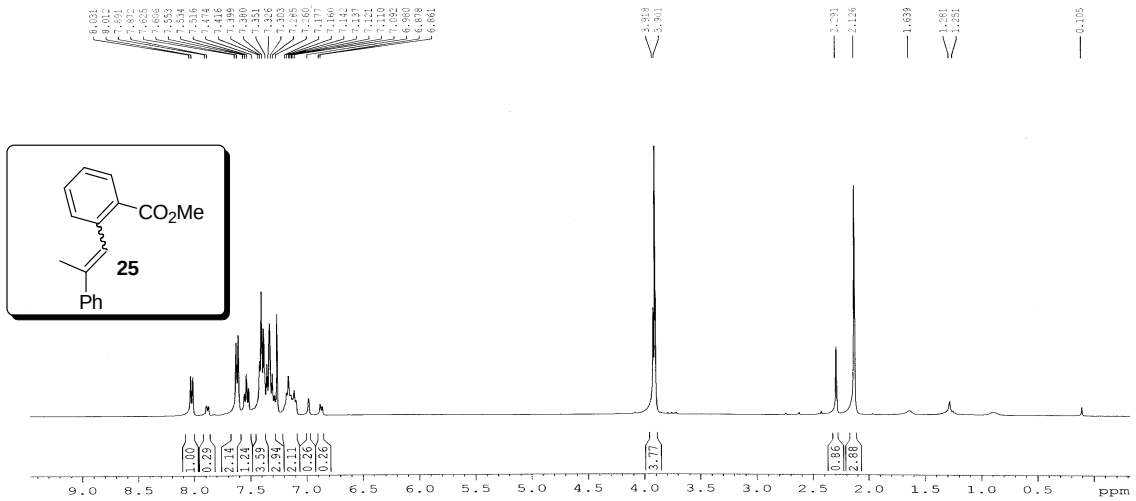


^{13}C NMR (100 MHz, $CDCl_3$):

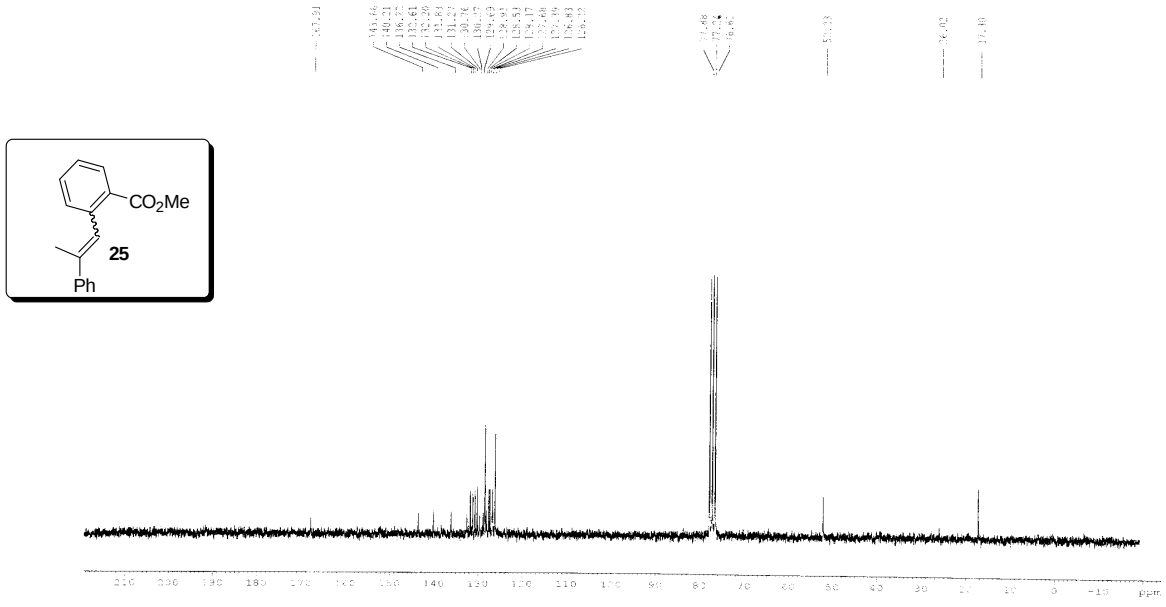


Methyl 2-(2-Phenyl-propenyl)benzoate (**25**):

^{1}H NMR (400MHz, $CDCl_3$):

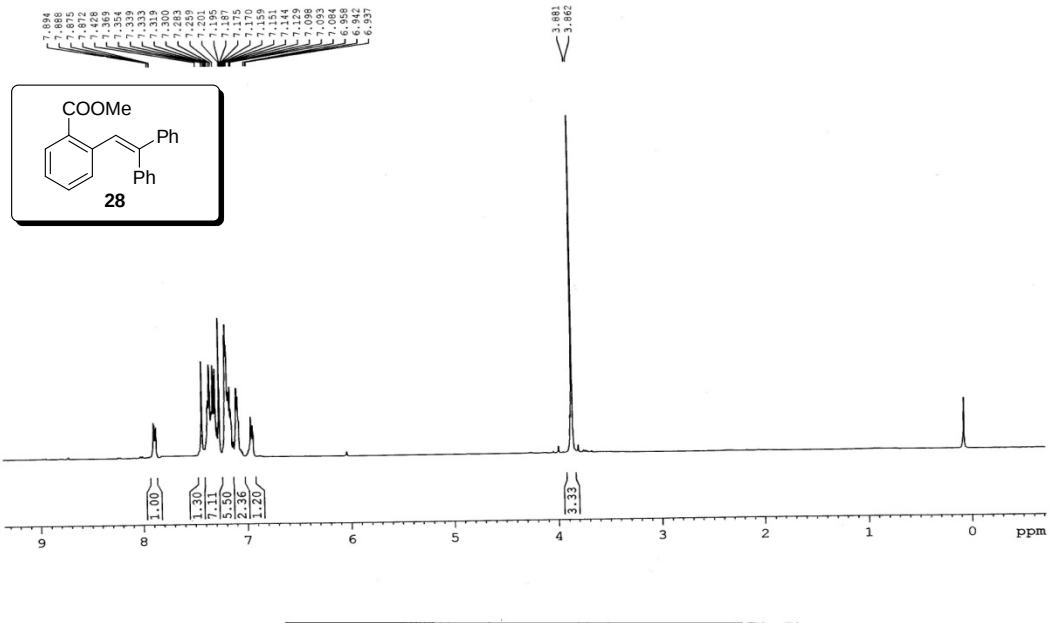


^{13}C NMR (100 MHz, $CDCl_3$):

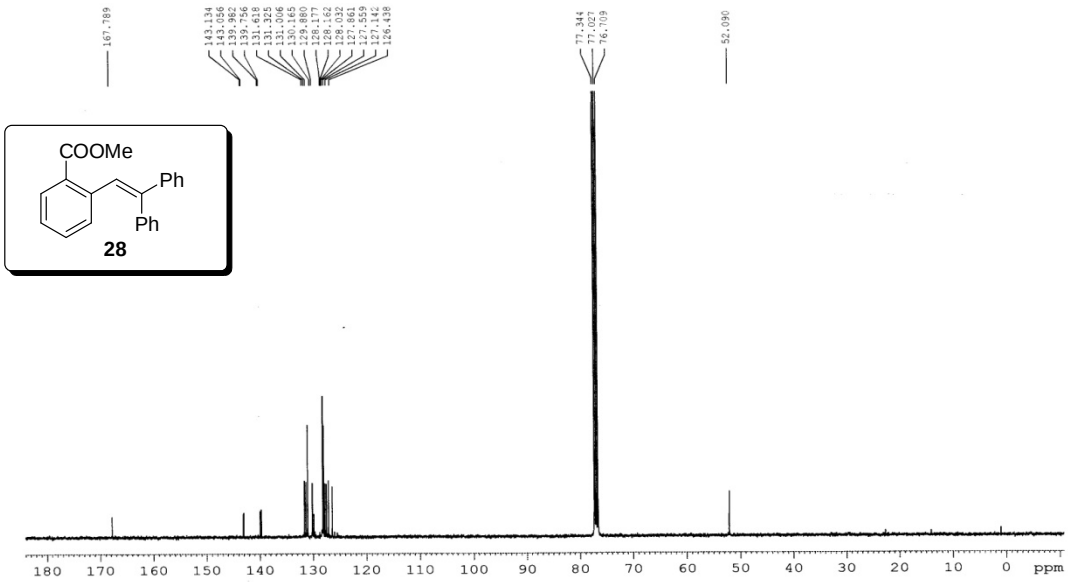


Methyl 2-(2,2 -Diphenyl-vinyl)benzoate (**28**):

^{1}H NMR (400MHz, $CDCl_3$):

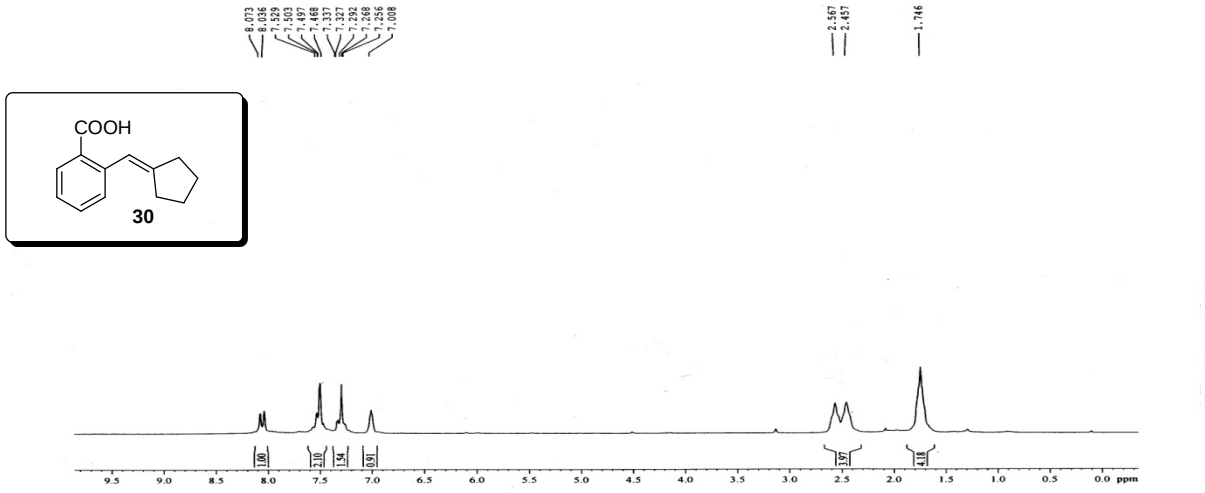


^{13}C NMR (100 MHz, $CDCl_3$):

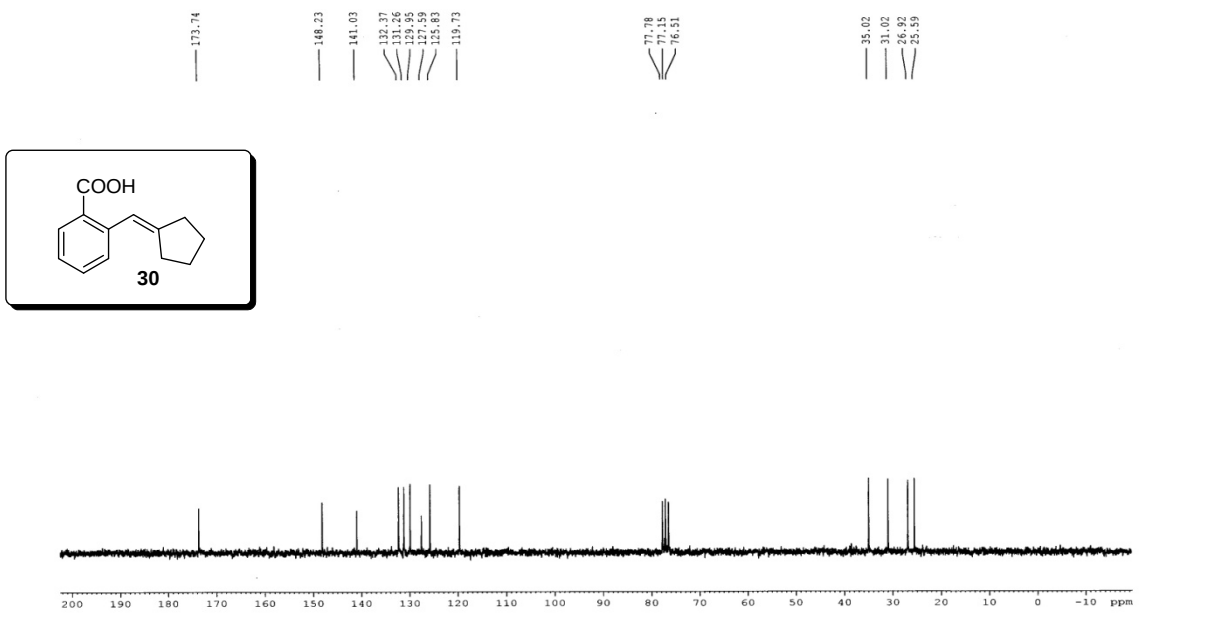


2-cyclopentylidenemethylbenzoic acid (**30**):

^{1}H NMR (200MHz, $CDCl_3$):

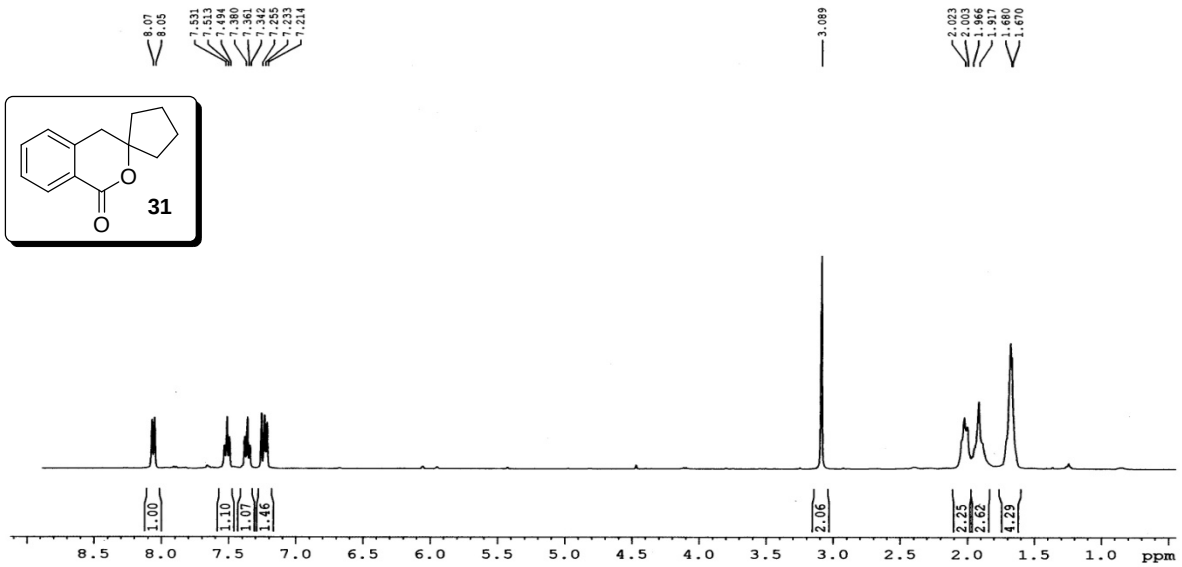


^{13}C NMR (50 MHz, $CDCl_3$):

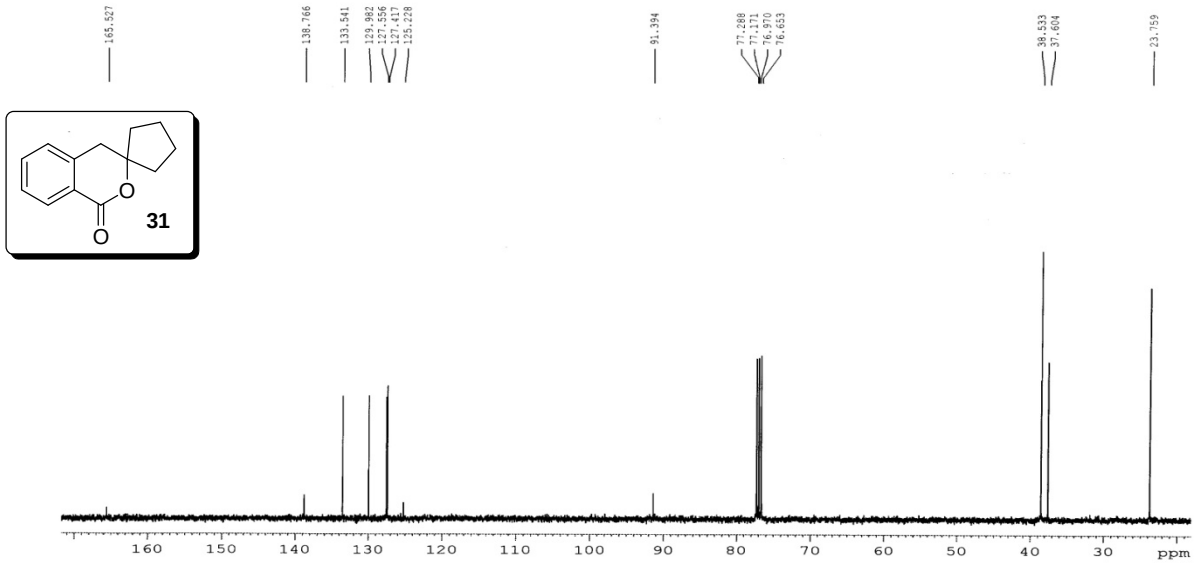


Spiro[3*H*-2-benzopyran-3,1'-cyclopentan]-1(4*H*)-one (**31**):

^{1}H NMR (400MHz, $CDCl_3$):

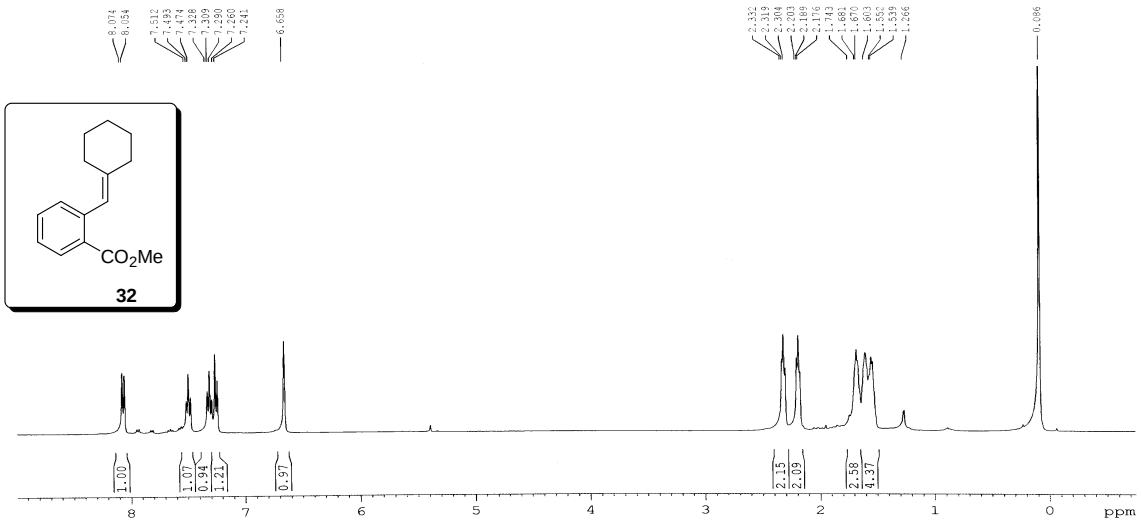


^{13}C NMR (100 MHz, $CDCl_3$):

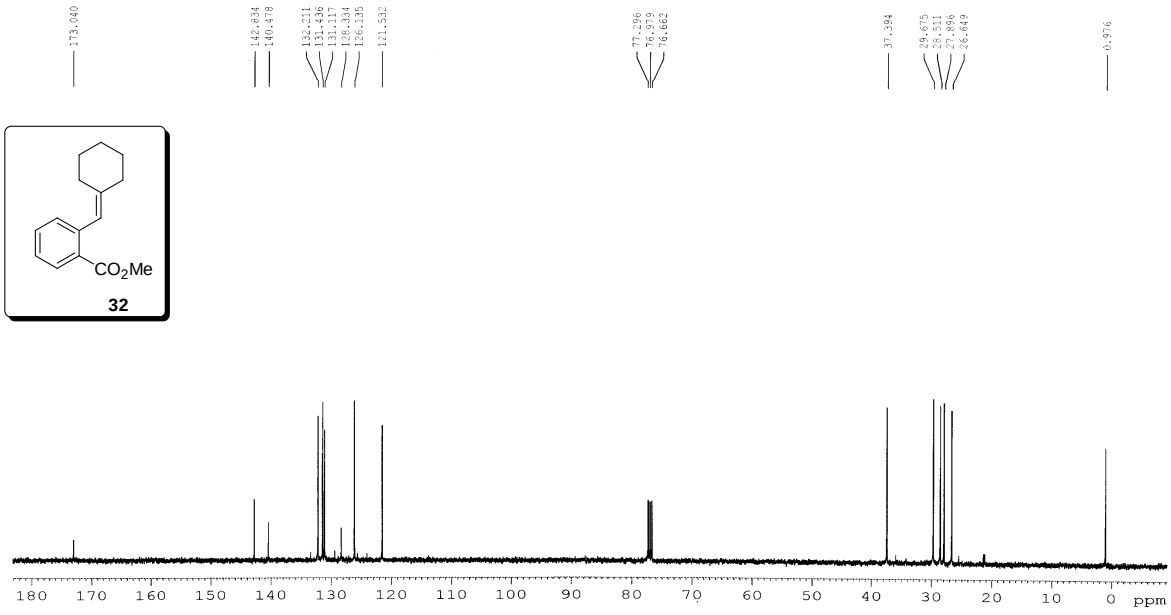


2-(Cyclohexylidenemethyl)benzoic acid (**32**):

^{1}H NMR (400MHz, $CDCl_3$):

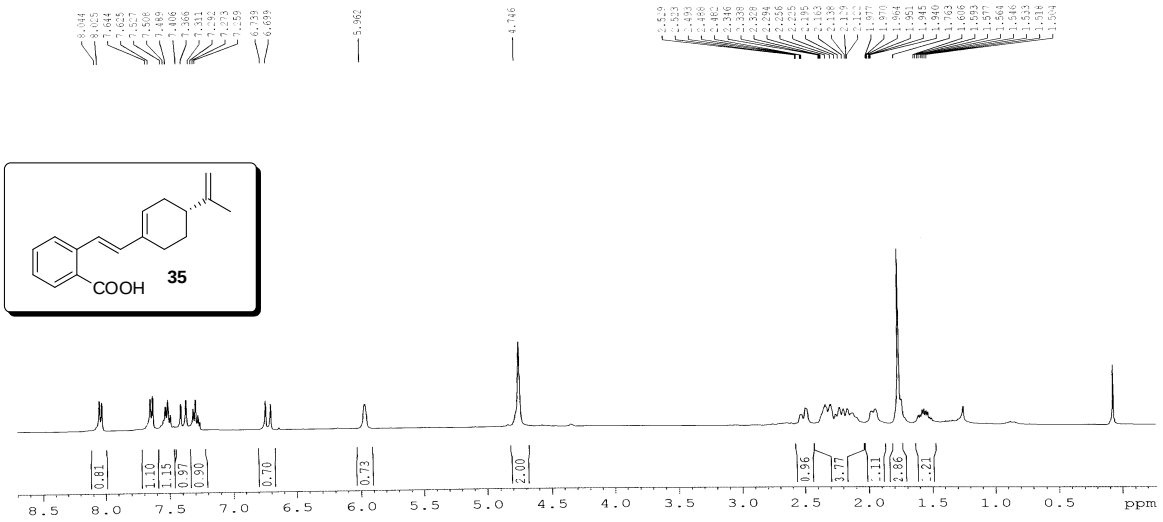


^{13}C NMR (100 MHz, $CDCl_3$):

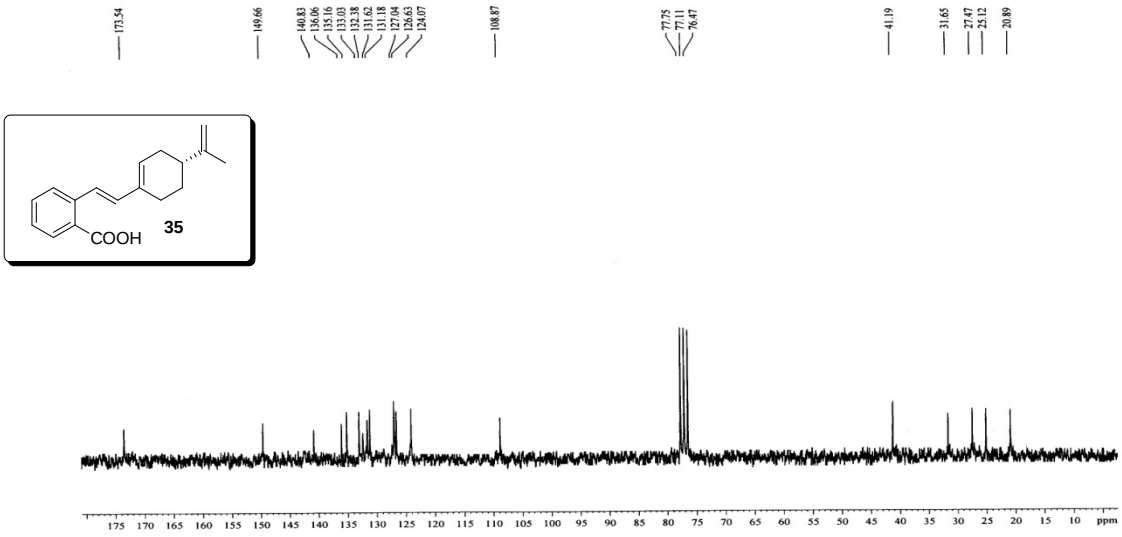


2-[2-(4-Isopropenylcyclohex-1-yl)vinyl]benzoic acid (**35**):

^{1}H NMR (400MHz, $CDCl_3$):

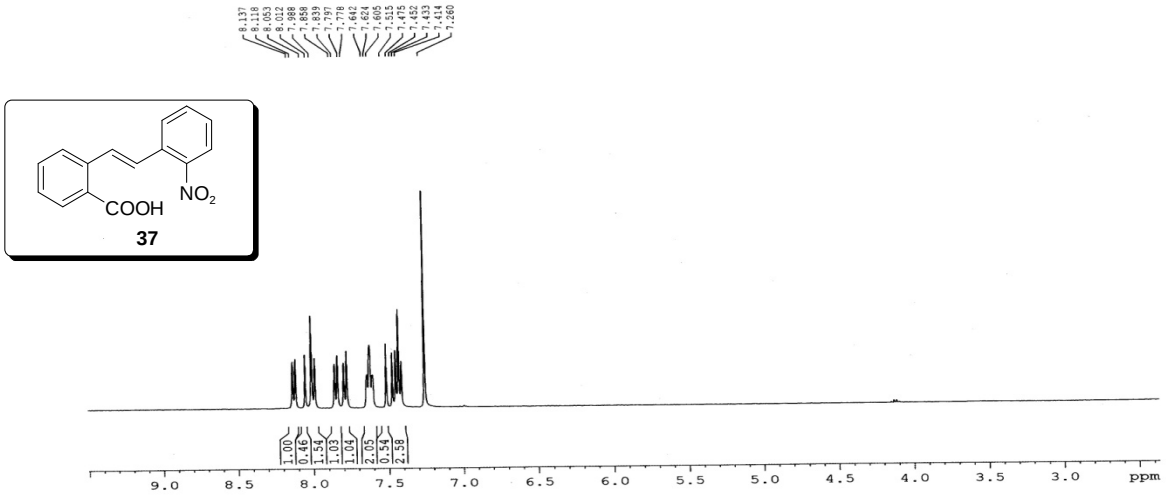


^{13}C NMR (50 MHz, $CDCl_3$):

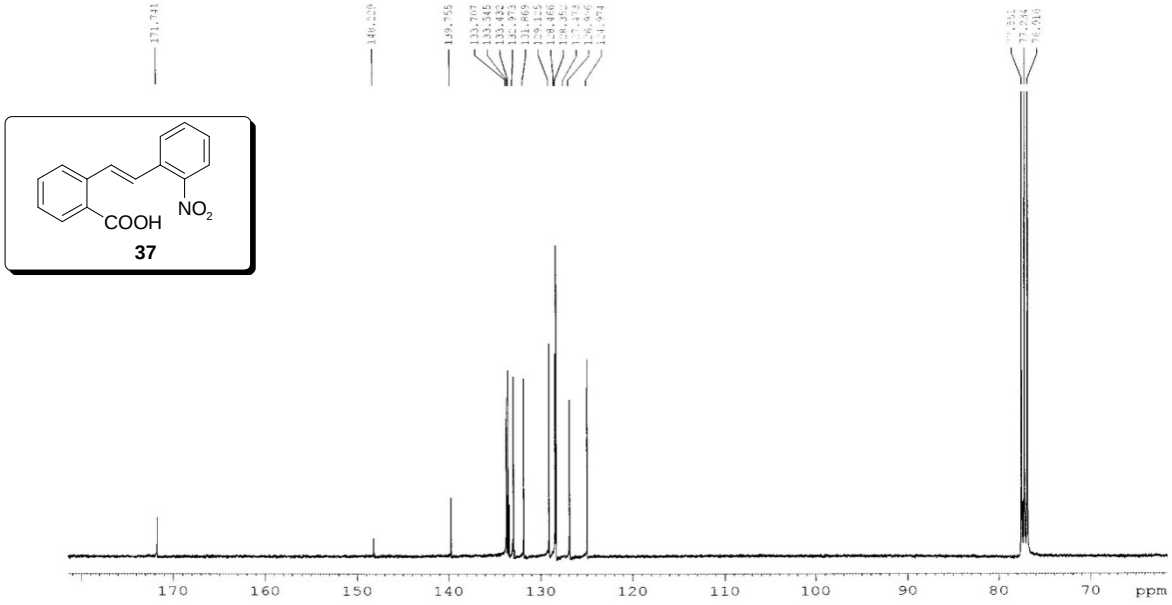


2-[2-(2-Nitrophenyl)vinyl]benzoic acid (**37**):

^{1}H NMR (400MHz, $CDCl_3$):

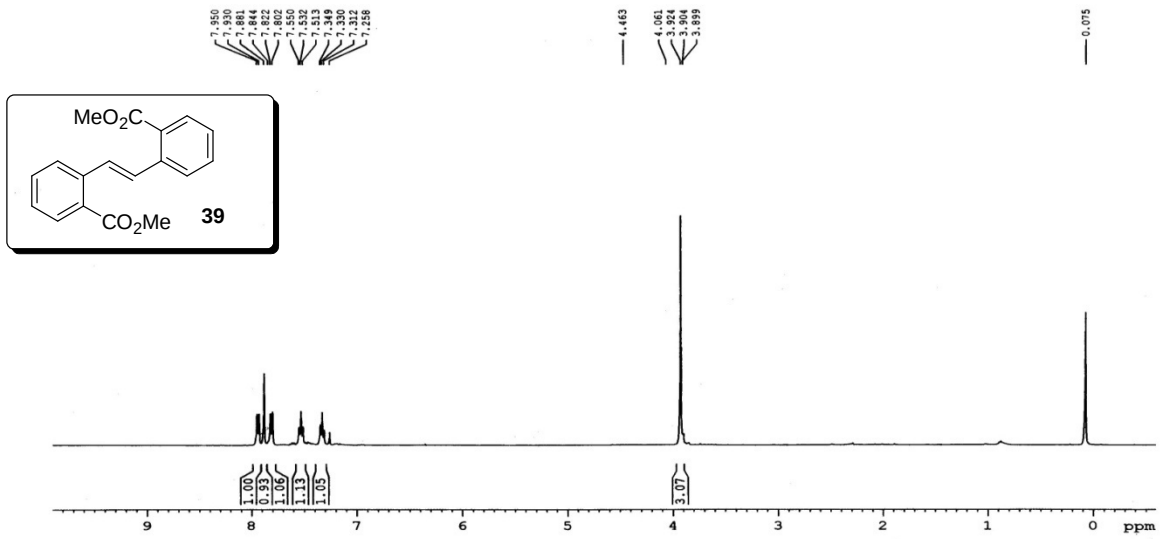


^{13}C NMR (100 MHz, $CDCl_3$):

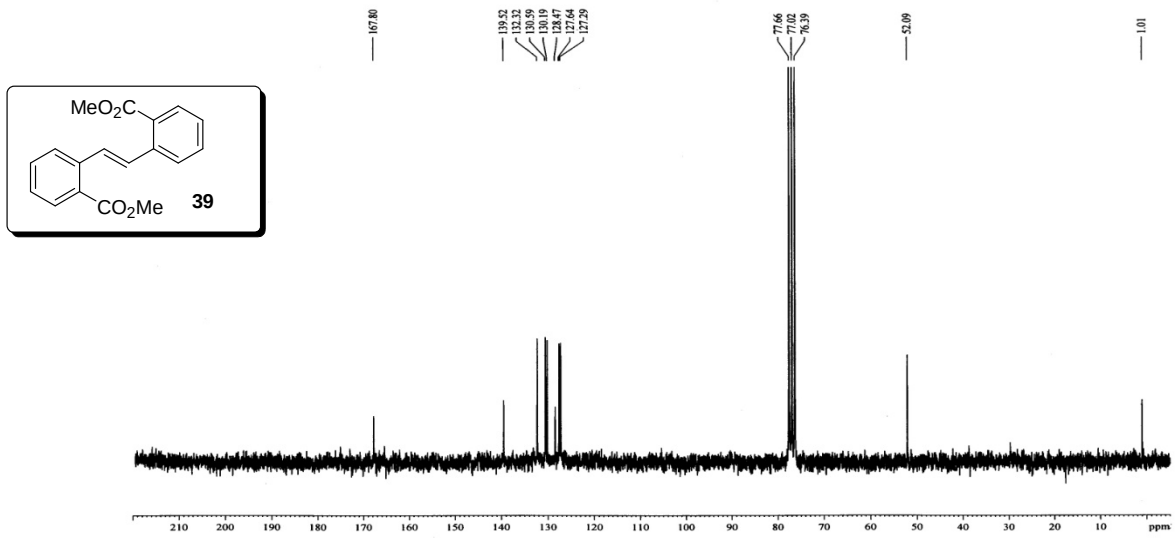


Benzoic acid, 2,2'-(1,2-ethenediyl)bis-, dimethyl ester (39):

^{1}H NMR (400MHz, $CDCl_3$):

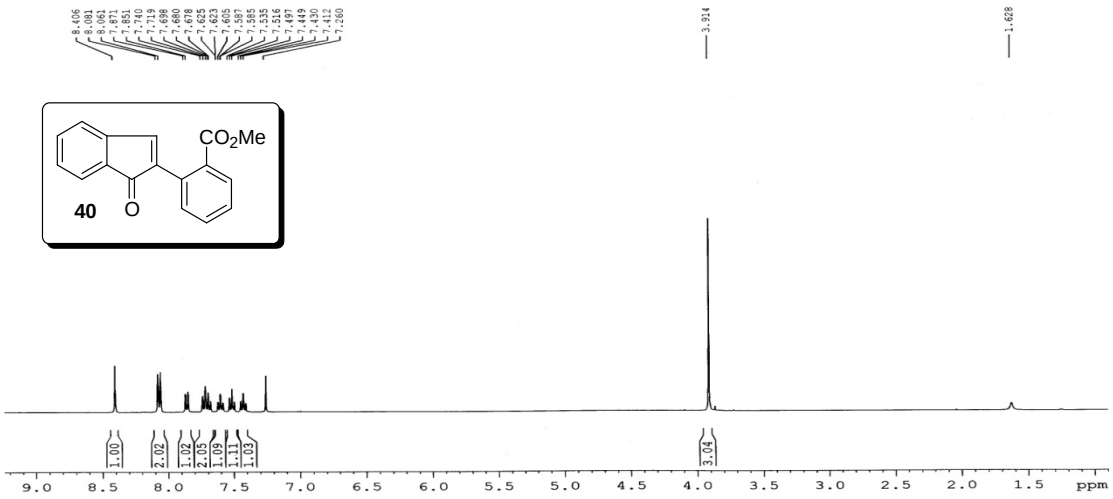


^{13}C NMR (100 MHz, $CDCl_3$):

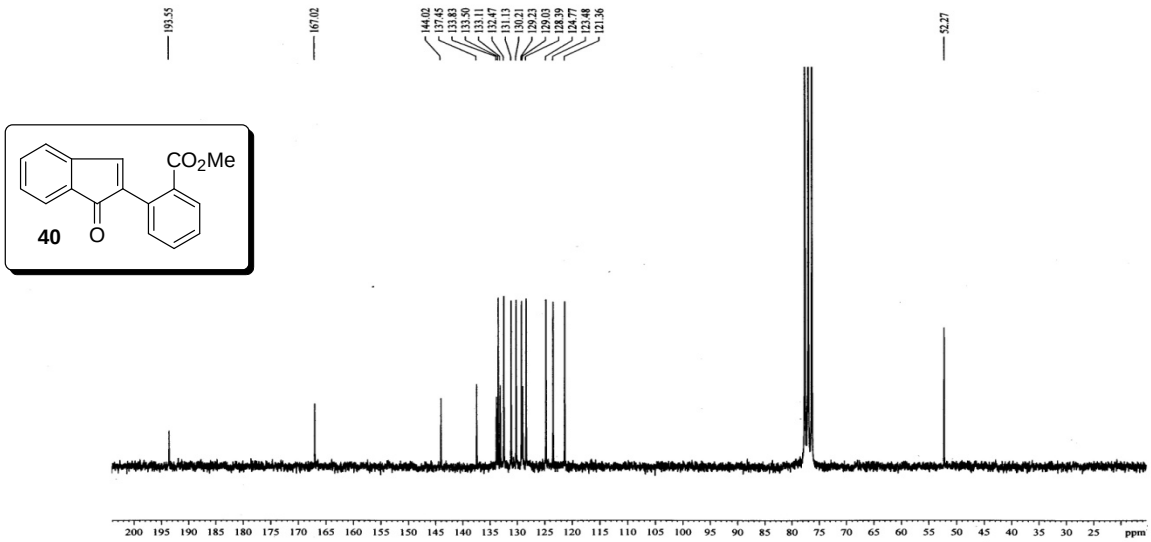


Methyl 2-(1-oxo-1*H*-inden-2-yl)benzoate (40):

^{1}H NMR (400MHz, $CDCl_3$):

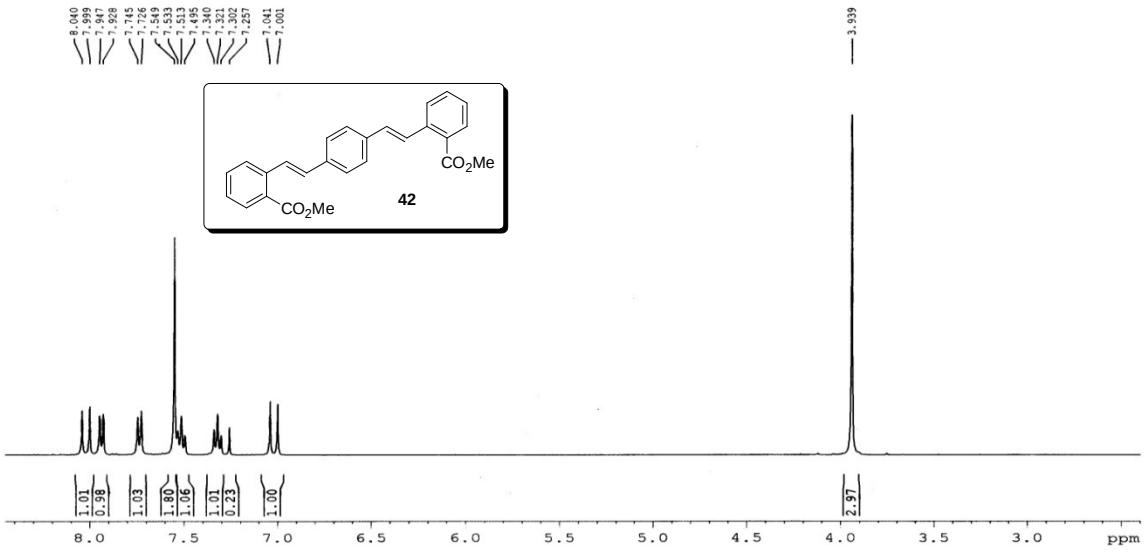


^{13}C NMR (100 MHz, $CDCl_3$):

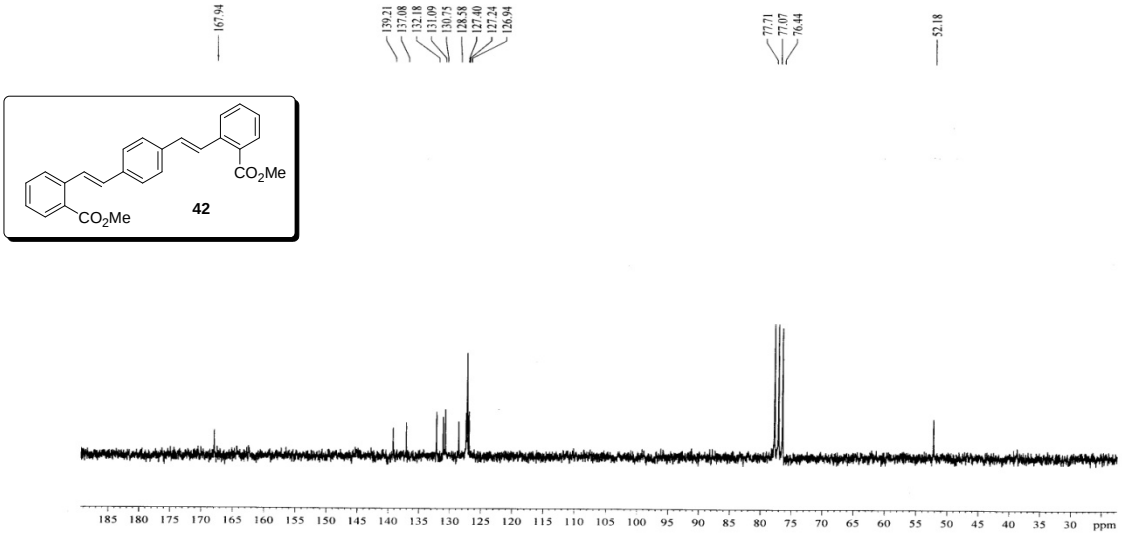


Dimethyl 2,2'-(1,4-phenylenedi-2,1-ethenediyl)bisbenzoate (**42**):

^{1}H NMR (400MHz, $CDCl_3$):

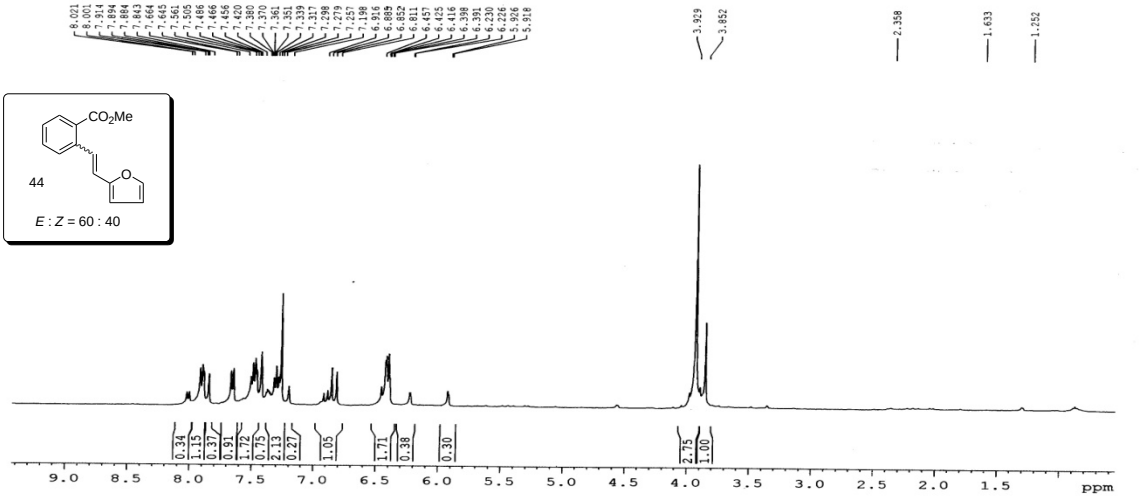


^{13}C NMR (100 MHz, $CDCl_3$):

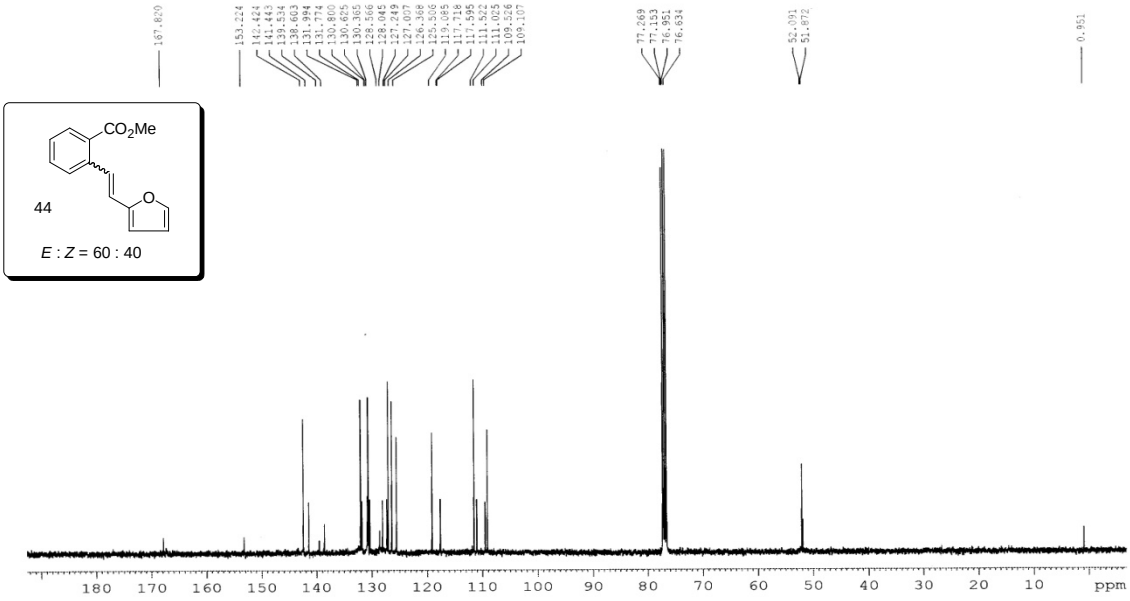


Methyl 2-(2-Furan-2-yl-vinyl)benzoate (**44**):

^{1}H NMR (400MHz, $CDCl_3$):

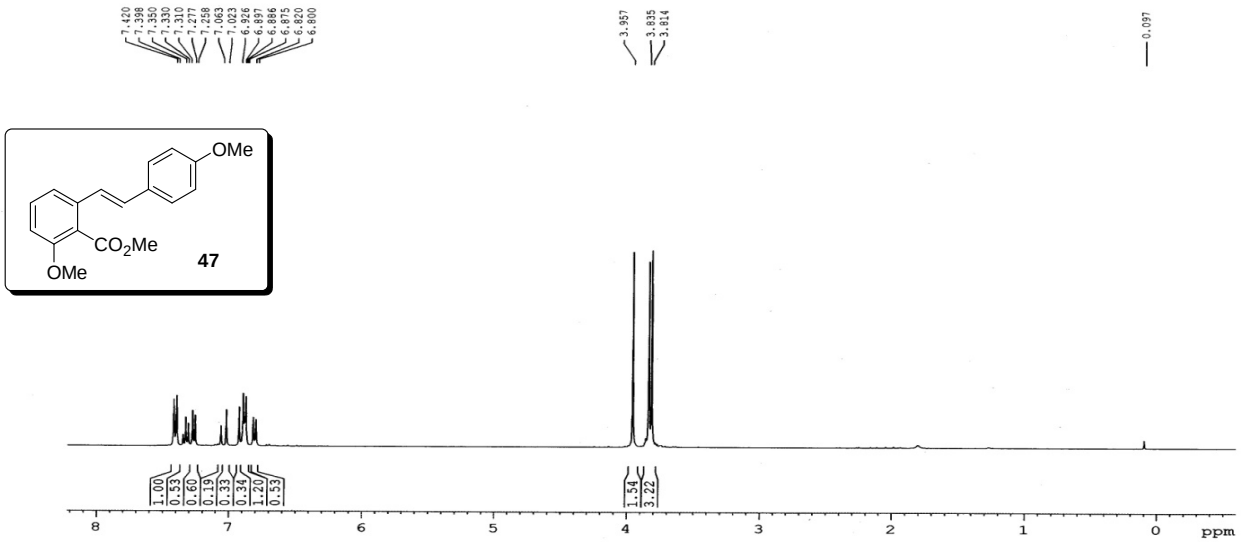


^{13}C NMR (100 MHz, $CDCl_3$):

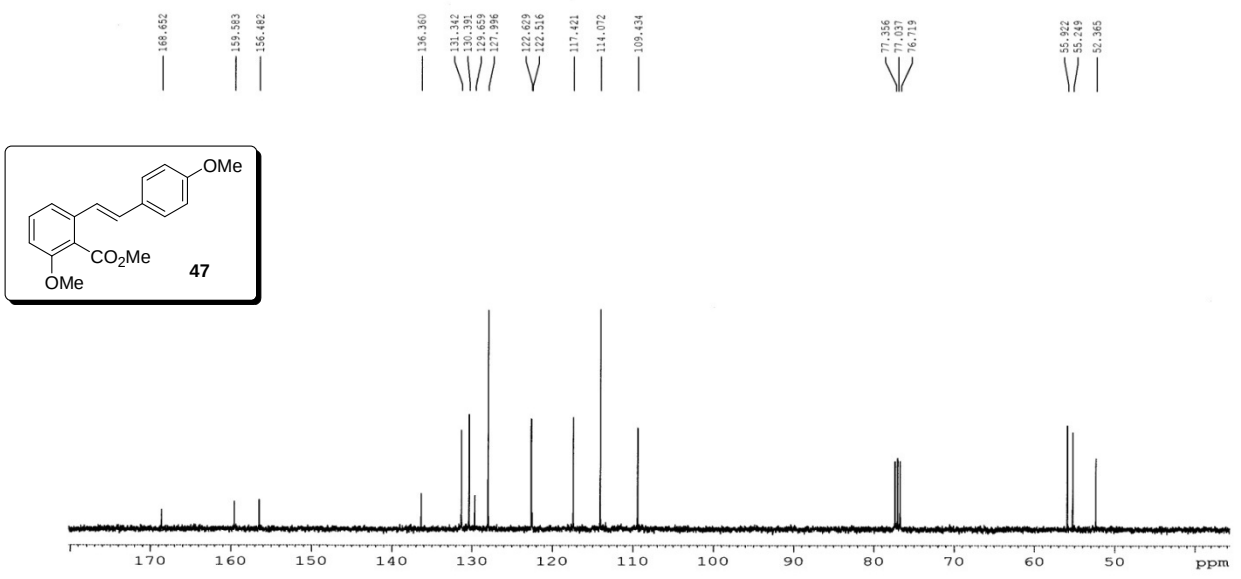


Methyl 2-methoxy-6-[2-(4-methoxyphenyl)ethenyl]benzoate (**47**):

^{1}H NMR (400MHz, $CDCl_3$):

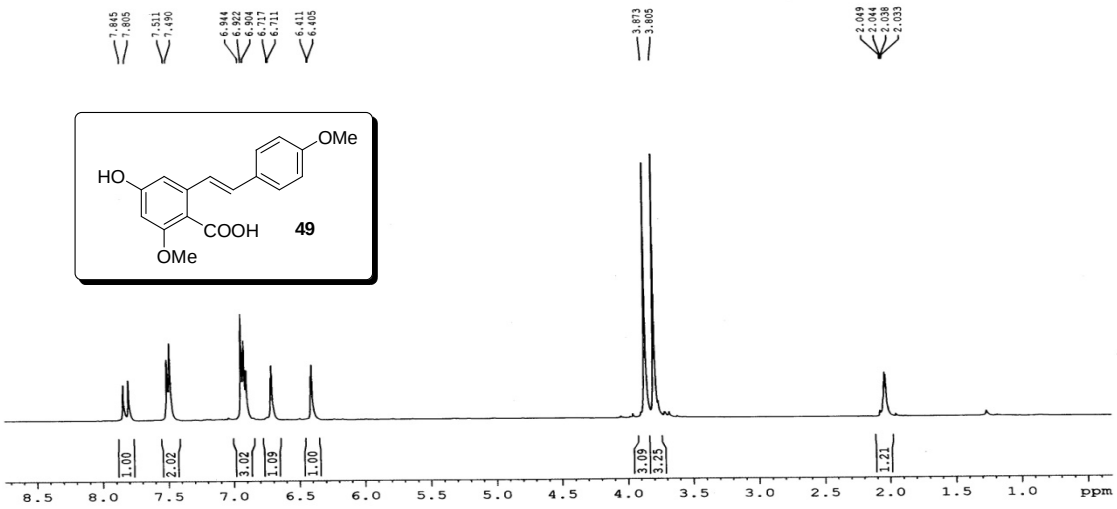


^{13}C NMR (100 MHz, $CDCl_3$):

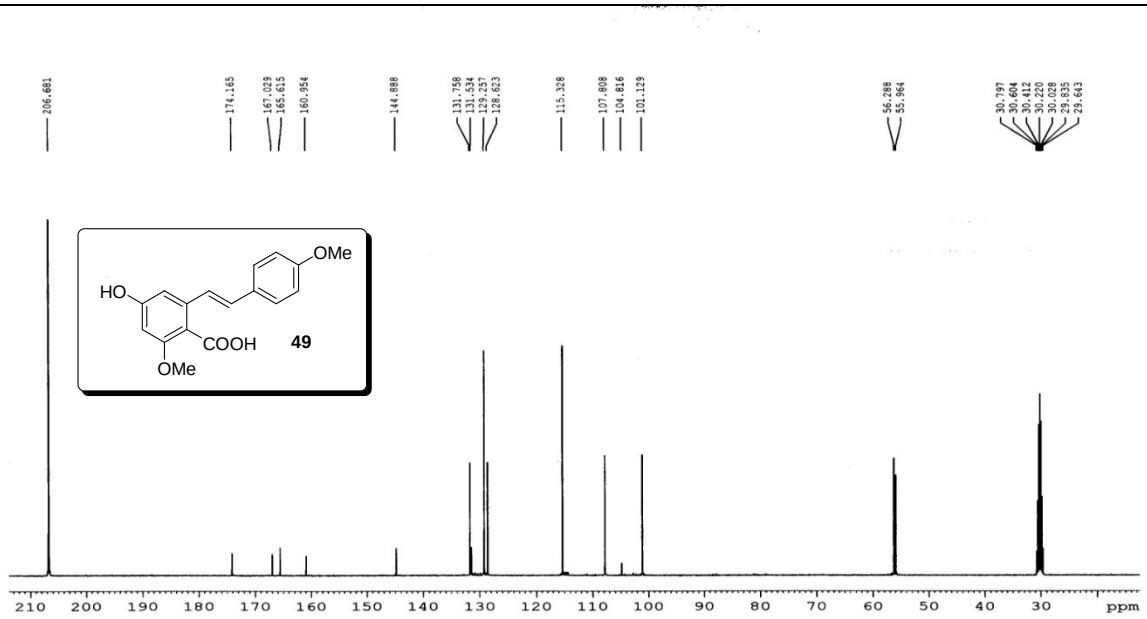


2-Hydroxy-4-methoxy-6-[2-(4-methoxyphenyl)vinyl]benzoic acid (**49**):

^{1}H NMR (400MHz, [D_6]-Acetone):

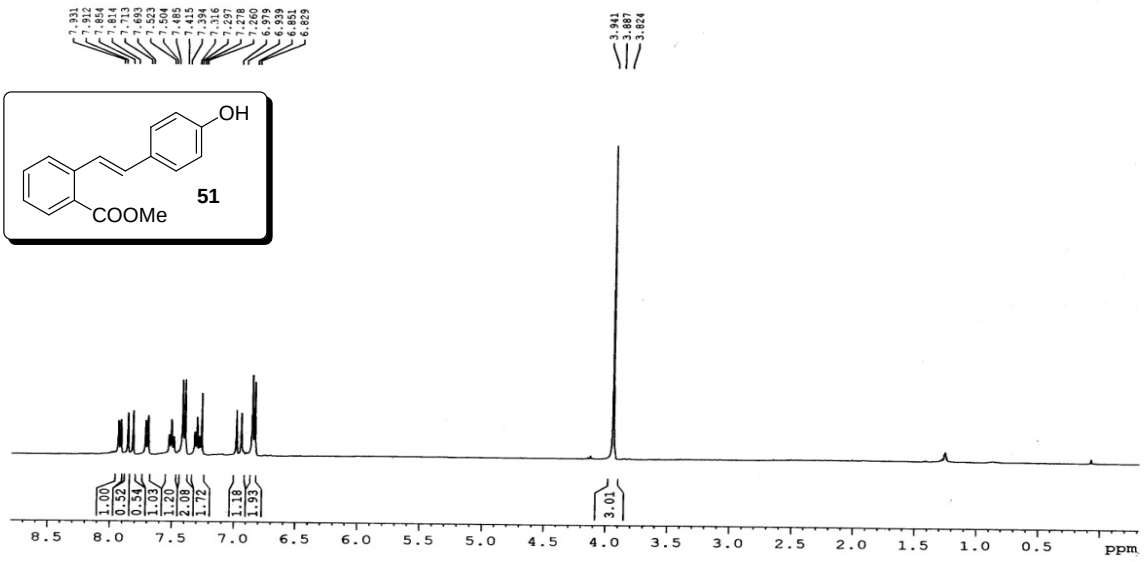


^{13}C NMR (100 MHz, [D_6]-Acetone):

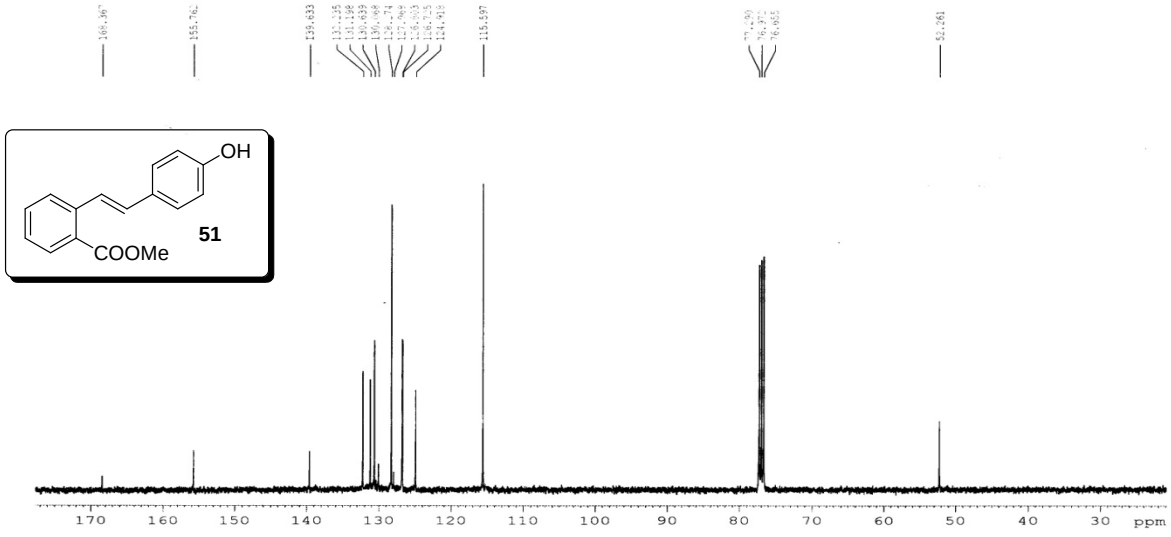


Methyl [2-(4-hydroxyphenyl)vinyl]benzoate (**51**):

^{1}H NMR (400MHz, $CDCl_3$):

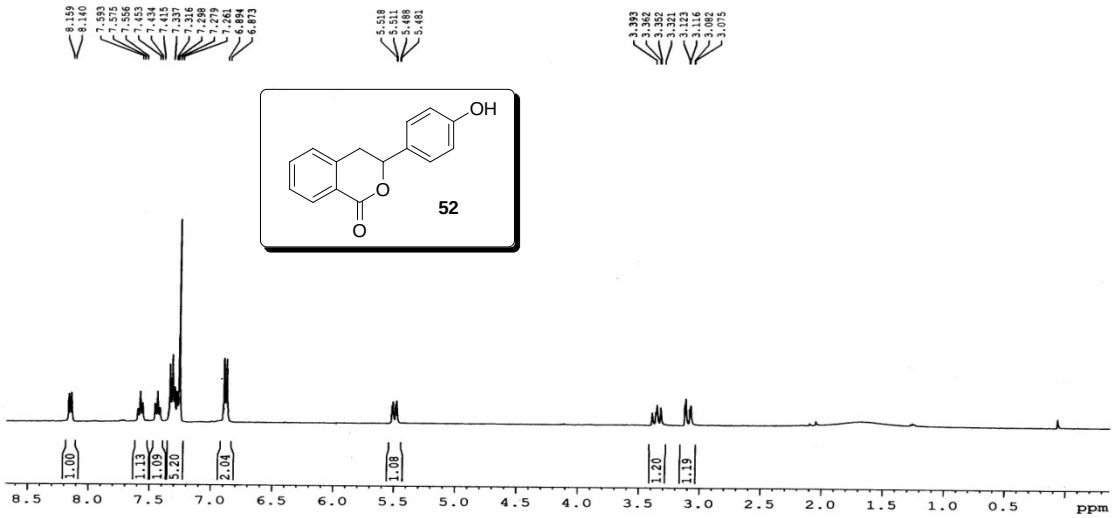


^{13}C NMR (100 MHz, $CDCl_3$):

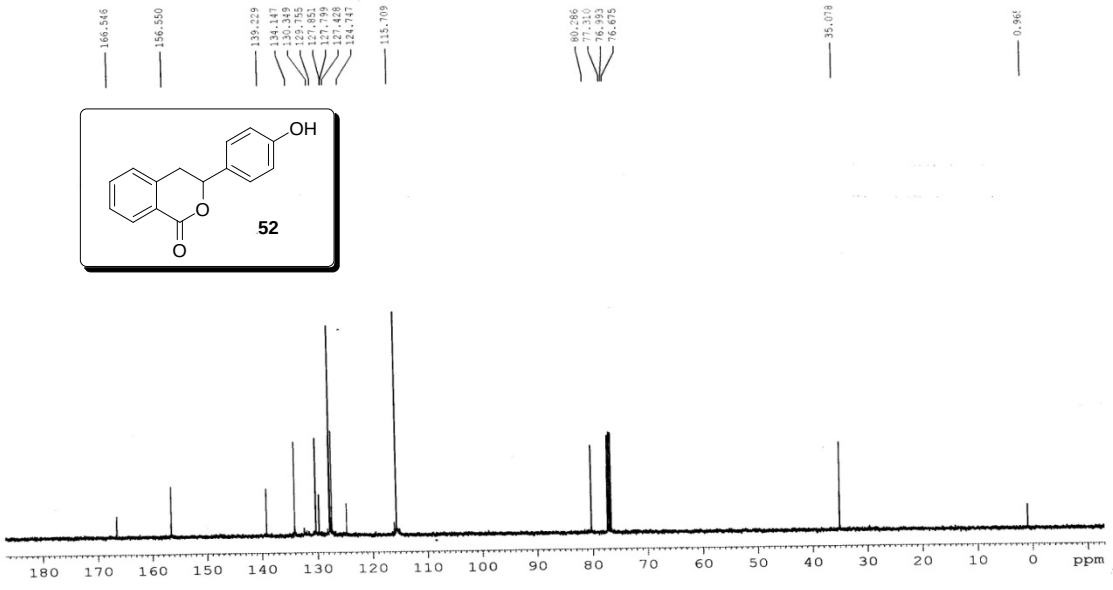


3-(4-Hydroxy-phenyl)-isochroman-1-one (**52**):

^{1}H NMR (400MHz, $CDCl_3$):

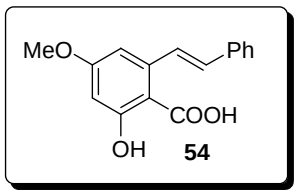


^{13}C NMR (100 MHz, $CDCl_3$):

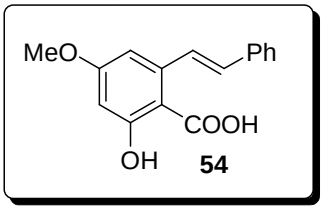


2-Hydroxy-4-methoxy-6-styrylbenzoic acid (54):

^{1}H NMR (400MHz, $CDCl_3$):

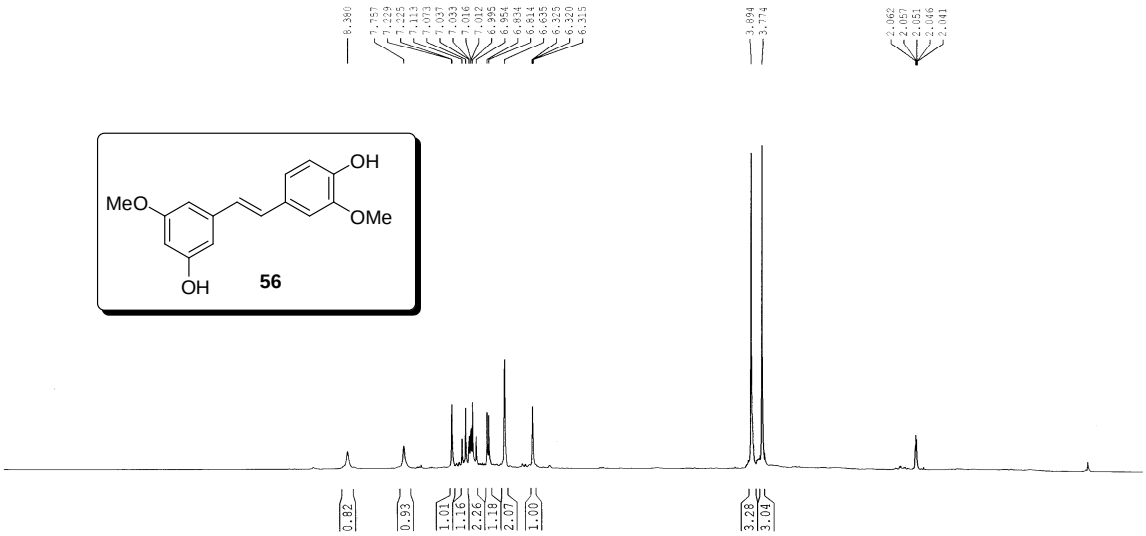


^{13}C NMR (100 MHz, $CDCl_3$):

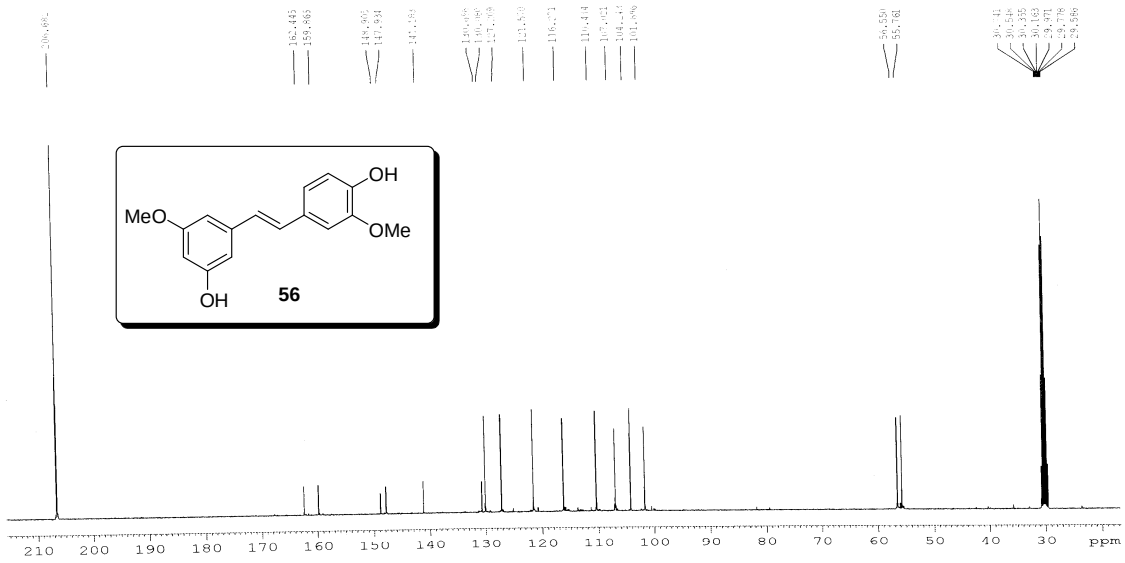


3',4-Dihydroxy-3,5'-dimethoxystilbene (**56**):

^{1}H NMR (400MHz, [D_6]-Acetone):

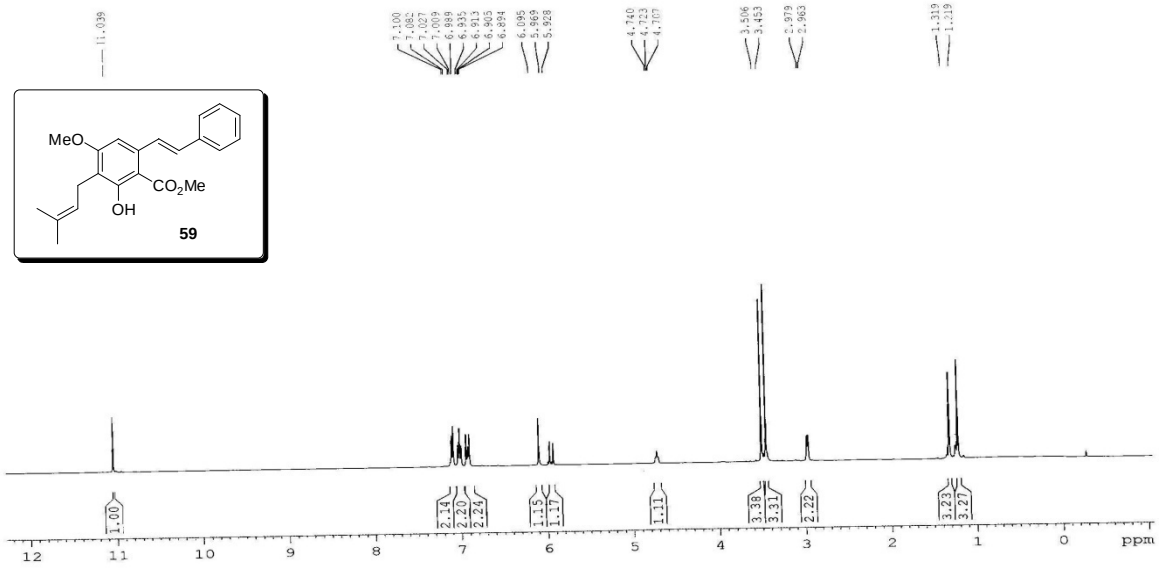


^{13}C NMR (100 MHz):

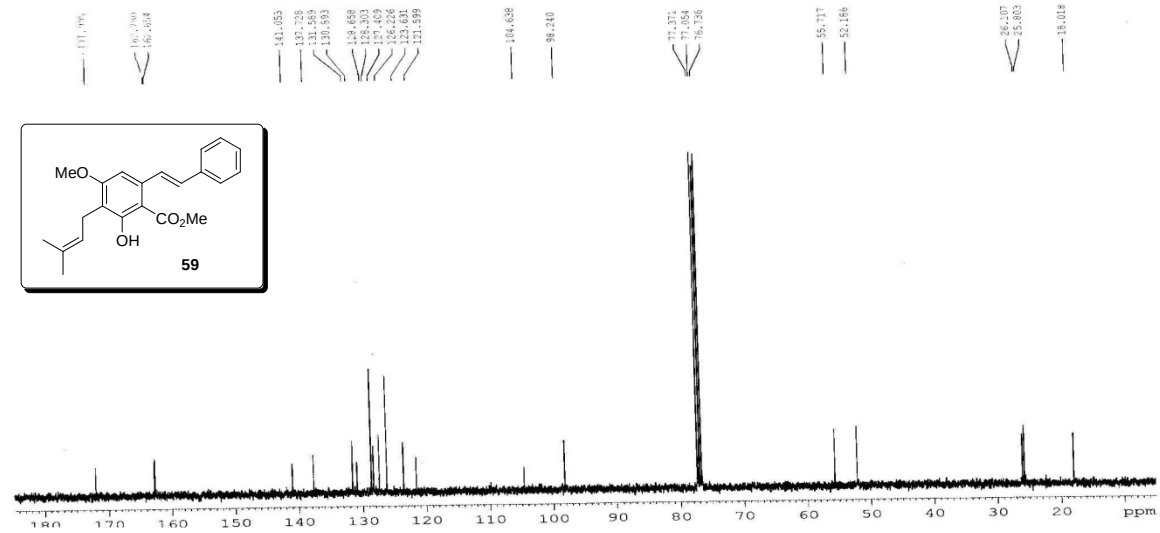


Methyl 2-hydroxy-4-methoxy-3-(3-methylbut-2-enyl)-6-styrylbenzoate (**59**):

^{1}H NMR (400MHz, $CDCl_3$):

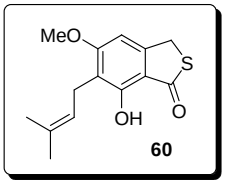


^{13}C NMR (100 MHz, $CDCl_3$):

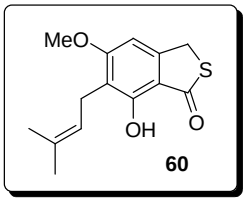


7-Hydroxy-5-methoxy-6-(3-methylbut-2-enyl)-3*H*-benzo[*c*]thiophen-1-one (**60**):

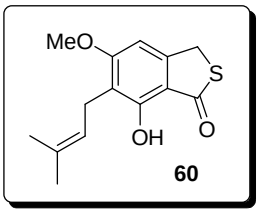
^{1}H NMR (200MHz, $CDCl_3$):



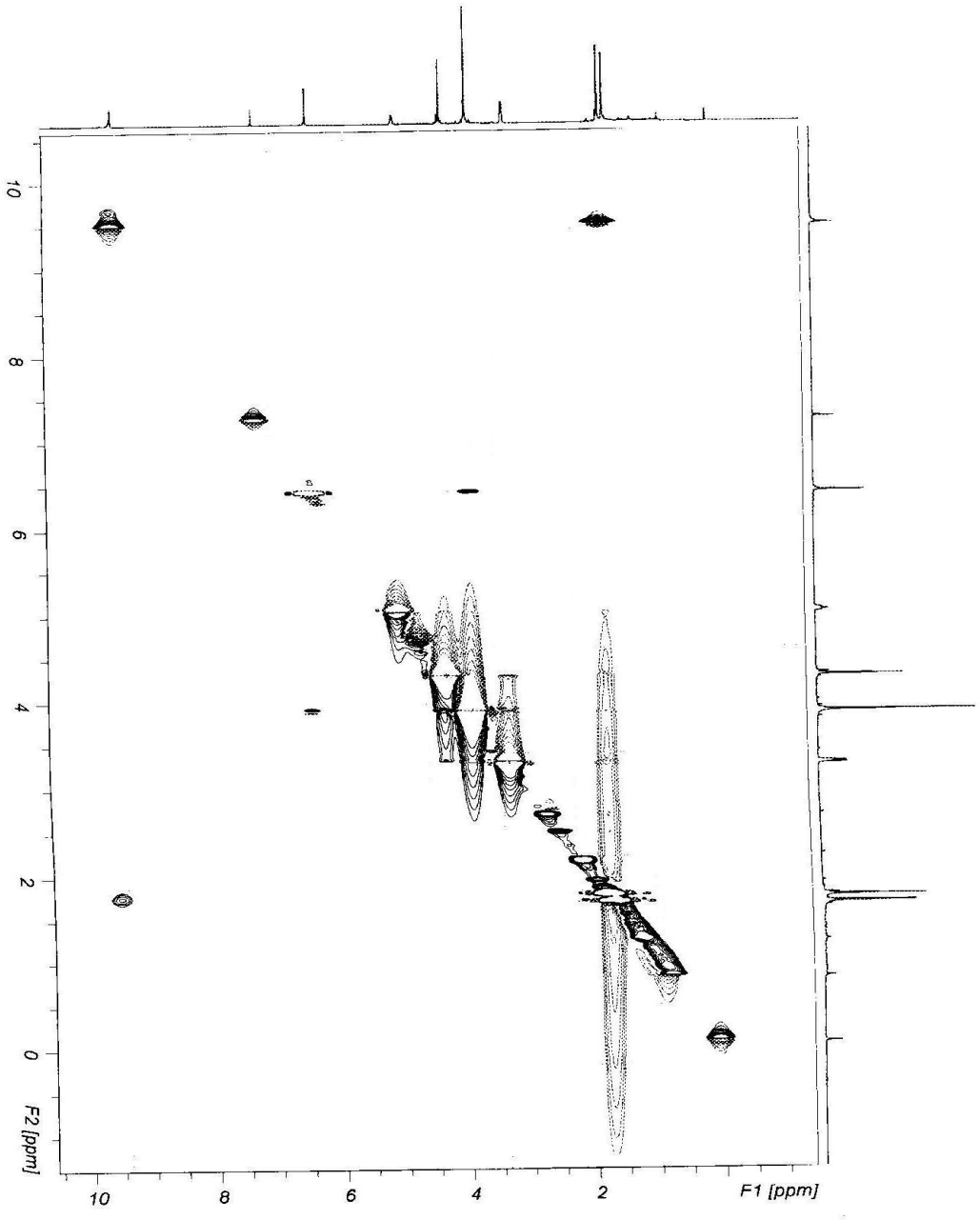
^{13}C NMR (50 MHz, $CDCl_3$):



NOESY NMR (400MHz, $CDCl_3$):



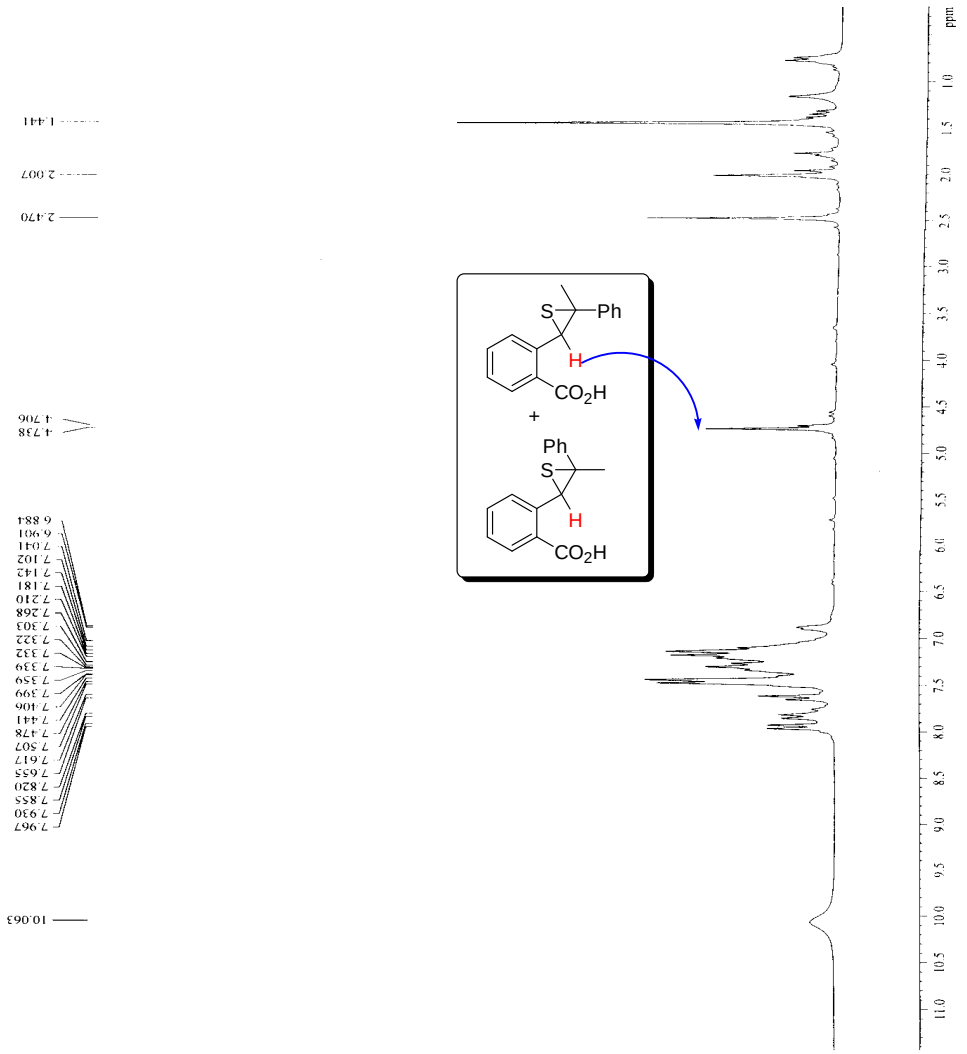
60



Rough ^{1}H NMR Spectral data of the compounds related to the mechanistic study:

^{1}H NMR spectrum of the crude reaction mixture between thiophthalide 8 and acetophenone 24:

^{1}H NMR (200MHz, $CDCl_3$):



3-(1-Methylsulfanyl-1-phenyl-ethyl)-*3H*-isobenzofuran-1-one (**64**):

^{1}H NMR (400MHz, $CDCl_3$):